# Enhanced Recovery After Surgery

Paul Hendry

MD

Department of Surgery, University of Edinburgh

2011

Dedicated to my beautiful wife Carol and our next big adventure together.

# Declaration

The present thesis was written and reference by me personally and the work described within undertaken by myself.

Some of the work was performed in collaboration:

Kerry Yuill, Senior Dietician, Edinburgh Royal Infirmary, performed analysis of food diaries.

Professor Tom Preston and Alexandra Small, Scottish Universities Environmental Research Centre, East Kilbride, UK, performed mass spectrometry analysis.

Magnetic Resonance Imaging was performed by John J. Totman and coordinated by Mr Dileep Lobo and Dr Luca Marciani, University of Nottingham, University Park, Nottingham, UK.

Dr Kees Dejong, Dr Ronald van Dam and Ms Stephanie Bukkems, Maastricht University Medical Centre and NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University, The Netherlands, coordinated the collection of perioperative data from study patients recruited in Maastricht.

The thesis was supervised by Professor Kenneth C.H. Fearon, University Department of Surgery, Edinburgh Royal Infirmary. Additional support was provided by Professor O.J. Garden, University Department of Surgery, Edinburgh Royal Infirmary.

Paul Hendry

# Acknowledgements

Many people played a significant role in the completion of this thesis and I am grateful to them all.

To Professor O.J. Garden, Professor S. Wigmore, Mr R Parks, Mr K.K. Madhavan, Mr E. Hidalgo, Mr J. Powell and Mr P. Ravindran for granting me access to the department and their patients. To the anaesthetists Dr D. Murphy, Dr B. Cook, Dr D. Cameron and Dr A. Lee who assisted in refining the perioperative care protocol and collecting perioperative data. To the nursing staff in the surgical wards of Edinburgh Royal Infirmary especially those in the High Dependence Unit who put the ERAS protocol into practice. To Sister Kirkpatrick and Joyce who assisted in the identification and location of study patients and provided numerous cups of tea. To Kerry Yuill, who provided invaluable dietetic advice and analysed the food diaries. To Angela Balfour who explained the reality of implementing a perioperative care pathway and always had useful advice. To David Francart and all of my research colleagues who provided assistance, advice and above all camaraderie.

To Professor Tom Preston and Alexandra Small in the Scottish Universities Environmental Research Centre for the mass spectrometry sample analysis and patient explanation of the stable isotope breath testing model (on more than one occasion). To Dr Kees Dejong, Dr Ronald van Dam, Dr Stephanie Bukkems and all of the team Maastricht University Medical Centre who allowed me to gain from their experience of enhanced recovery programmes and collaborated in the running of a multi-centre trial. To Mr Dileep Lobo, Dr Luca Marciani, John Totman, Jeff Wright, Mr Gabriel

Rodrigues and all of the staff at Queens Medical Centre and Sir Peter Mansfield Magnetic Resonance Centre in Nottingham for sharing their expertise in MR imaging and postoperative gastric emptying.

To the all the members of the ERAS group in particular Dr Kristoffer Lassen, Dr Jonatan Hausel, Dr Jonas Nygren and Dr Olle Ljungqvist for unrestricted use of their data and general support.

To all of the patients in Edinburgh and Maastricht who kindly agreed to participate, without whom surgical research would not be possible. Their universal agreement to participate and enthusiasm for the study during a clearly stressful time period was humbling.

To Professor Ken Fearon, whose enthusiasm never faltered and whose 'gentle nudges' were essential to the completion of this thesis. Thank you for switching the lights on when I got lost in the dark.

# Contents

## *LIST OF PUBLICATIONS*

**Hendry P**, Balfour A, Potter MA, Mander BJ, Bartolo DC, Anderson DN, Fearon K. Preoperative conditioning with oral carbohydrate loading and oral nutritional supplements can be combined with mechanical bowel preparation prior to elective colorectal resection. *Colorectal Dis* 2008;**10**(9): 907-10.

van Dam RM, **Hendry PO**, Coolsen MM, Bemelmans MH, Lassen K, Revhaug A, Fearon KC, Garden OJ, Dejong CH. Initial experience with a multimodal enhanced recovery programme in patients undergoing liver resection. *Br J Surg* 2008;**95**(8): 969-975.

**Hendry PO**, Hausel J, Nygren J, Lassen K, Dejong CH, Ljungqvist O, Fearon KC, on behalf of the Enhanced Recovery After Surgery (ERAS) Study Group. Determinants of outcome after colorectal resection within an enhanced recovery programme. *Br J Surg* 2009;**96**(2): 197-205.

Lobo DN, **Hendry PO**, Rodrigues G, Marciani L, Totman JJ, Wright JW, Preston T, Gowland P, Spiller RC, Fearon K. Gastric emptying of three liquid oral preoperative metabolic preconditioning regimens measured by magnetic resonance imaging in healthy adult volunteers: A randomised double-blind, crossover study. *Clin Nutr* 2009;**28**(6): 636-41

**P. O. Hendry**, R. M. van Dam, S. F. F. W. Bukkems, D. W. McKeown, R. W. Parks, T. Preston, C. H. C. Dejong, O. J. Garden and K. C. H. Fearon on behalf of the Enhanced Recovery After Surgery (ERAS) Group. Randomized clinical trial of laxatives and oral nutritional supplements within an enhanced recovery after surgery protocol following liver resection. *Br J Surg* 2010;**97**(8): 1198-206.

## *LIST OF ABBREVIATIONS*

| | |
|---|---|
| ASA | American Society of Anesthesiologists grade |
| BMI | Body Mass Index |
| CCD | Clear Carbohydrate Drink |
| CHO | Carbohydrate |
| cPDR | Cumulative percentage dose recovered |
| ERAS | Enhanced Recovery After Surgery |
| GE | Gastric emptying |
| IGF-1 | Insulin like growth factor |
| IRMS | Isotope Ratio Mass Spectrometry |
| MBP | Mechanical Bowel Preparation |
| MR | Magnetic Resonance |
| ONS | Oral Nutritional Supplements |
| $PDRh^{-1}$ | Percentage dose recovered per hour |
| PONV | Postoperative nausea and vomiting |
| POSSUM | Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity |
| RNI | Recommended nutritional intake |
| SIBT | Stable Isotope Breath Test |
| TIVA | Total Intravenous Anaesthetic |

## *ABSTRACT*

The Enhanced Recovery After Surgery model of perioperative care targets the obstacles to recovery following major abdominal surgery: pain, gastrointestinal dysfunction and immobility. This model of care combines elements that have individually been shown to attenuate the surgical stress response, reduce postoperative analgesia requirement or maintain perioperative nutrition. Through combining these elements it has been possible to improve early postoperative function and reduce the requirement for hospital stay with an unaltered or even reduced complication rate.

Within the available ERAS studies subjective postoperative outcomes are employed and it is difficult to assess the true contribution of many of the individual protocol elements to postoperative recovery. The reduction in length of stay, in itself, may represent more efficient use of inpatient care rather than an improved rate of functional recovery. Further refinement and validation of the ERAS model will be achieved by establishing randomised controlled trials that test its feasibility and effectiveness within other surgical specialties, establish objective, reproducible outcome measures and examine the specific contribution of individual protocol elements within the ERAS protocol. It is expected that further improvement in postoperative recovery may specifically rely on reducing gut dysfunction in the early postoperative period. The establishment of randomised controlled trials and objective endpoints will facilitate testing individual element that target gastrointestinal recovery.

This thesis demonstrates that the application of an ERAS model of care to hepatic surgery is feasible and results in a reduction in postoperative stay similar to that seen in colorectal surgery. This suggests that the ERAS programme of care may be extrapolated to other surgical specialties. The present thesis also demonstrates that activity meters and stable isotope gastric empting breath tests can be employed in the early postoperative period to provide objective measures of postoperative recovery. Most significantly this thesis demonstrates through a randomised controlled trial that within an ERAS protocol early routine administration of laxatives can improve postoperative rate of gastrointestinal recovery following hepatic resection.

## SUMMARY OF THESIS

The ERAS programme aims to reduce postoperative organ dysfunction and the requirement for inpatient hospital stay through a series of perioperative measures that abate the stress response to surgery. The present thesis describes the concept of the surgical stress response and the current knowledge base for the ERAS protocol in colorectal surgery. It then explores the application of such a protocol in liver resection, potential benefits for higher risk patients, the development of novel objective outcome measures and the significance of perioperative nutritional conditioning and postoperative laxation within an ERAS protocol.

**Chapter 1** describes the pathophysiological response to surgery and its negative impact on postoperative recovery. The evidence for individual elements of the ERAS protocol is explored along the overall benefits of a combining such elements. The limitations of the existing evidence base are also described. Finally, the potential role of routine laxation and oral nutritional supplements administered in the early postoperative period within an overall ERAS programme is discussed along with potential objective endpoints to better gauge the success of enhanced recovery programmes.

Many ERAS trials present small, single hospital series. The ERAS study group is an international collaboration of five European centres each contributing to a prospective database providing a multi-centre, prospective database of over 1000 patients was available. This database was examined to determine the overall safety of the ERAS programme and to assess its potential benefit for higher risk patients specifically the

elderly, undernourished and those with significant comorbidity. In **Chapter 2** of the present thesis the ERAS programme of care is shown to promote faster postoperative recovery for 1035 patients undergoing colorectal resection within an ERAS programme of care. A median hospital stay of 6 days is achieved with a readmission rate of 8·6 percent and a morbidity rate lower than predicted by P-POSSUM. Against this background of favourable clinical outcomes, neither poor nutritional status (BMI below 20 $kg/m^2$), nor advanced age (80 years or more) were independent predictors of postoperative 30 - day morbidity or mortality. These findings suggest that within an ERAS programme the surgeon does not need to individualize postoperative morbidity or mortality risk assessment for elderly or undernourished patients. In contrast, comorbidity was a consistent independent determinant for all outcomes.

The ERAS model has been developed mainly within colorectal surgery. Although other areas of surgery have adapted the ERAS approach (orthopaedics, vascular), upper gastrointestinal and hepatobiliary surgery remains relatively under-researched. In **Chapter 3** a multimodal ERAS programme for patients is demonstrated to be safe and effective for 61 patients undergoing liver resection. Fifty-six patients in the ERAS group tolerate fluids within four hours of surgery, median time to commencing oral diet is one day compared with three in the control group ($P < 0·001$) and median time to discharge is six days compared with eight in the control group ($P < 0·001$). These outcomes were achieved without any significant increase in readmission rate, morbidity or mortality.

In order to develop ERAS programmes further, novel outcome measures are required to assess postoperative gastrointestinal function and overall functional recovery

objectively. In **Chapter 4** 32 patients underwent stable isotope breath testing (SIBT) on postoperative day three following hepatic resection and managed within an ERAS programme of care. SIBT is demonstrated to be a feasible postoperative test to examine liquid gastric emptying as a measure of postoperative recovery. A link between delayed gastric emptying and delayed hospital discharge is suggested.

Early mobilisation is a key component of the ERAS protocol. Activity monitoring can document patients' mobility in he early postoperative period and act as a measure of recovery. In **Chapter 5** the use of postoperative physical activity monitoring is evaluated in 50 patients in the early postoperative period following hepatic resection within an ERAS programme of care. Physical activity monitoring is shown to be a feasible method of assessing recovery in the early postoperative period. Patients following an ERAS programme of care demonstrate a prompt increase in activity level in the early postoperative phase and early step count appears to correlate with length of hospital stay.

Preoperative conditioning is a significant part of any ERAS programme. One element of this preparation is to send the patient to theatre in a metabolically fed state. Traditionally, not only have patients been fasted, they have also been given mechanical bowel preparation. Whilst MBP has been largely abandoned for colonic procedures there are occasions when it is still desirable. Currently use of MBP precludes feeding. In **Chapter 6** the use of preoperative carbohydrate and fluid loading are demonstrated to be feasible for patients also receiving mechanical bowel preparation. In a prospectively audited group of 147 patients receiving MBP, 83 % of

patients were able to complete the prescribed ONS, 80 % the prescribed CHO/fluid loading and 74 % completed both.

A further concept in preoperative preparation is to provide additional metabolic conditioning agents along with carbohydrate loading. There are, however, questions related to the gastric emptying profile and therefore safe preoperative administration of any new preparation. In **Chapter 7** the gastric emptying rate of a new beverage containing glutamine and antioxidants in two concentrations is evaluated and compared with an existing and widely used clear carbohydrate beverage in a three-way crossover study of 20 healthy volunteers using MR imaging. MR imaging confirms complete emptying of the clear carbohydrate solution from the stomach within 120 minutes and therefore its suitability to be administered up to two hours prior to anaesthesia as any other clear fluid. The new beverage, however, required 180 minutes to empty from the stomach in both 300 ml and 400 ml concentrations and therefore cannot be safely administered as a 'clear fluid'.

The evidence for many of the individual elements of the ERAS protocol has been established within traditional care. There is a need to examine which elements are significant when employed within an overall ERAS package. In **Chapter 8,** 74 patients were recruited to a 2 x 2 factorial study evaluating the effect of routine postoperative laxation, postoperative nutritional supplements and their potential interaction within an ERAS programme of care. In this study routine postoperative laxation is shown to expedite gastrointestinal recovery within an ERAS protocol for patients undergoing liver resection. This resulted in an earlier first passage of stool. There was not any additional benefit demonstrated when laxation is combined with

preoperative carbohydrate loading and postoperative oral nutritional supplements. Overall, patients following the ERAS protocol recommenced oral fluid intake on the same day as surgery, had started eating the day after surgery and were fully mobile by the third postoperative day. They had achieved discharge criteria on the fourth postoperative day and median length of hospital stay was 6 days. There was no further improvement in overall rate of recovery beyond that achieved within the ERAS programme for the groups receiving laxation or nutritional supplements.

This thesis demonstrates the clinical safety and efficacy of ERAS when applied to both colorectal and hepatobiliary surgery. The first randomised trial of a protocol element within an ERAS programme is presented along with novel, objective endpoints to allow further protocol development. It would appear that ERAS represents an important step forwards for perioperative care. There is both the potential to develop such a programmes in different surgical models and to further refine the ERAS protocol for a more effective recovery.

# SECTION A. HYPOTHESIS AND AIMS

Through targeting the key elements that delay postoperative hospital discharge, pain, immobility and gut dysfunction, the ERAS programme has been shown to promote earlier recovery following major colorectal surgery. These benefits are achieved with a similar or even reduced incidence of postoperative morbidity. The elderly, undernourished and infirm population are at particular risk following postoperative complications and therefore would have most to gain from any intervention that can successfully reduce postoperative morbidity. It is currently unclear if such benefits can be achieved in these high-risk patients.

To further test and refine the ERAS protocol it should be applied to other surgical specialties. It is currently unclear if such a model of care will be feasible for all surgical specialities and if similar improvements in postoperative outcomes can be achieved. Due to the fact that postoperative outcomes following hepatic resection are relatively predictable the establishment of an ERAS-liver care pathway is likely to provide a suitable model in which to further test the individual elements of the ERAS protocol within randomised controlled trials.

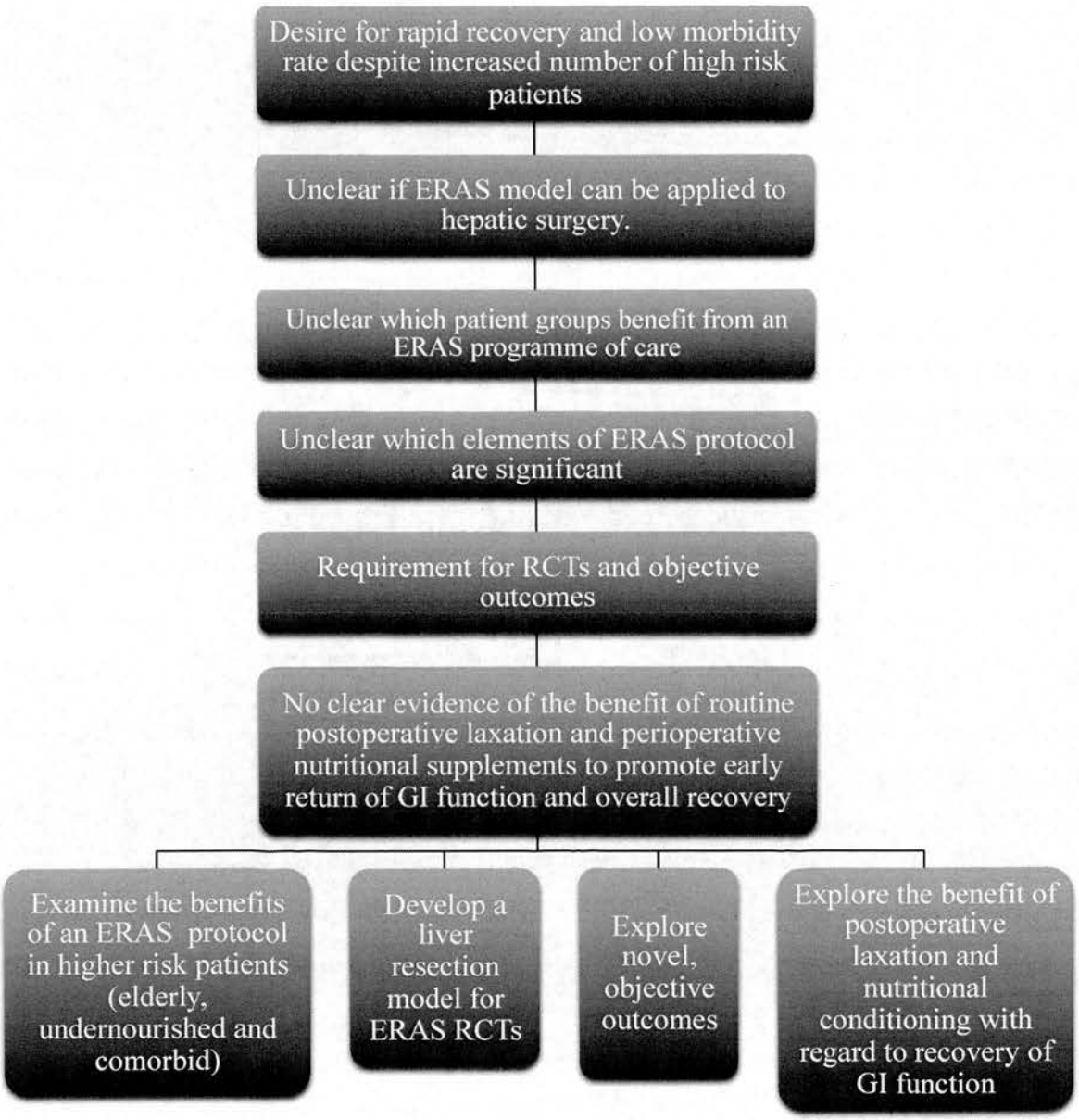
Much of the evidence for individual elements of the ERAS package has been established within traditional perioperative care. Although the overall ERAS package has been shown to be of benefit it is not clear which of the elements employed are of most significance. Within existing ERAS studies the outcomes employed as endpoints are often subjective or in effect markers of protocol compliance. Few objective markers exist to allow appropriate comparison between perioperative interventions. The development of suitable, objective endpoints and structured randomised

controlled trials within a background of an ERAS care pathway will provide a more scientific measure of the significance of individual protocol elements.

Future improvements in postoperative recovery rate are likely to be gained by optimising gastrointestinal function in the early postoperative period and increasing oral intake. Preoperative carbohydrate drinks are one element employed within ERAS that has been demonstrated to reduce the negative metabolic effects of surgery. New preoperative drinks, which combine glutamine and antioxidants with carbohydrate, may provide further benefits, however, their gastric emptying profile is unknown and it may not be safe to administer these drinks in the same time frame as existing carbohydrate only drinks.

The aims of this thesis are to explore the feasibility of an ERAS package of care in other surgical specialties, examine its benefits in higher risk groups and assess the safety of a novel preoperative, conditioning drink. Through a randomised controlled trial this thesis aims to assess the specific contribution of combining routine postoperative laxation with preoperative nutritional conditioning and postoperative nutritional supplements to promote earlier recovery of gastrointestinal functional and therefore overall functional recovery. This is summarised in Figure 1.1.

**Figure 1.1 Overview of thesis aims and objective.**



## Hypotheses

1. **The benefits of the ERAS approach to perioperative care are applicable to all patient groups including those traditionally at higher risk.**

2. **The ERAS protocol can be safely applied to patients undergoing hepatic resection.**

3. **Hepatic resection can provide a suitable human model for randomised controlled trials in enhanced recovery.**

4. **Gastric emptying and activity level can provide objective postoperative outcomes for future trials of enhanced recovery protocols.**

5. **Administration of preoperative, metabolic conditioning drinks in combination with mechanical bowel preparation is safe and feasible.**

6. **Preoperative drinks combining carbohydrate with additional metabolic conditioning elements (glutamine and antioxidants) can be safely administered to patients two hours prior to surgery**

7. **Enhanced recovery of gastrointestinal function combined with use of oral nutritional supplements and preoperative carbohydrate and fluid loading may optimise recovery of postoperative nutritional status and physical function following hepatic resection.**

To establish if the improved postoperative outcomes demonstrated within an ERAS pathway could be achieved by all patient groups, including those traditionally at higher risks (advanced age, undernourished or those with significant comorbidity), a cohort study of 1035 patients undergoing colorectal resection within an enhanced recovery after surgery programme was explored. This included data on patient demographics, perioperative management and postoperative outcomes (including time to achieve targeted mobility, total length of hospital stay, complications and 30-day mortality) and was collected prospectively across a number of centres. The outcomes for specific groups of patients with adverse nutritional risk (body mass index (BMI) below 20 kg/m2), advanced age (80 years or more) and comorbidity (American Society of Anesthesiologists (ASA) grade III–IV) are discussed in Chapter 2.

A pilot study of patients undergoing liver resection within an ERAS care pathway was performed to examine both its feasibility in such a group and to develop a predictable model for future randomised controlled trials. A consecutive series of sixty-one patients, undergoing hepatic resection, followed an ERAS protocol modified for hepatobiliary surgery. Postoperative outcomes were compared with a consecutive series of patients undergoing surgery within a traditional care pathway. The feasibility of the enhanced recovery protocol and a comparison of the endpoints for both groups are discussed in Chapter 3.

The potential role of gastric emptying and physical activity as objective markers of postoperative recovery was assessed in patients undergoing hepatic resection within an ERAS pathway. A stable isotope breath testing technique, suitable for bedside testing was used to measure liquid gastric emptying on postoperative day three and a

discrete, patient worn accelerometer device used to record physical activity between postoperative days 3 - 9 and 30 - 40. The results obtained from both techniques were compared with other traditional postoperative outcomes in Chapters 4 and 5.

To determine the feasibility of administering preoperative metabolic conditioning drinks and protein supplements in combination with mechanical bowel preparation where necessary, a cohort of patients receiving such a combination of preoperative interventions is presented in Chapter 6.

To guide the safe administration of a novel preoperative metabolic conditioning regimen containing glutamine and antioxidants, a randomised, crossover study was performed. This compared the gastric emptying times of two concentrations of the novel drink with a widely available carbohydrate only preparation using magnetic resonance imaging. This is presented in Chapter 7

To establish the potential role of routine postoperative laxation to promote early recovery of gastrointestinal function within an ERAS programme and then assess the potential interaction of such an improvement with a combination of preoperative carbohydrate/ fluid loading and postoperative oral nutritional supplementation, a randomised controlled trial was performed. This two-by-two factorial study is presented in Chapter 8.

## SECTION B. INTRODUCTION

## *Chapter 1. Enhanced Recovery After Surgery concept*

This chapter briefly outlines the surgical stress response and its metabolic sequelae following uncomplicated major abdominal surgery, the concept of the Enhanced Recovery After Surgery programme and its potential role in both colorectal and hepatic surgery. The limitations of existing datasets, the evidence base for specific elements of the ERAS protocol and the subjective outcome measures currently employed in most of the existing trials are also discussed.

The future direction of the ERAS programme and therefore potential improvements in both rate of postoperative recovery and morbidity are likely to depend on optimising perioperative gastrointestinal function. This chapter assesses the role of the existing protocol elements to promote early recovery of gastrointestinal function and discusses the limitations in the current models used to test such elements. Evidence to support the use of routine postoperative laxation within an enhance recovery of gastrointestinal function is examined along with its potential combination with preoperative carbohydrate/ fluid loading and postoperative oral nutritional supplementation to improve overall functional recovery.

## 1.1 The surgical stress response and metabolic sequelae.

Cuthbertson originally described an orchestrated stress response to trauma, characterised by a period of catabolism (Cuthbertson, 1930;Cuthbertson, 1931). In the period following major surgery there is a similar period of hypermetabolism, malaise and potentially organ dysfunction due to activation of the endocrine, metabolic and inflammatory systems (Wilmore, 2002).

The endocrine response is activated by afferent neuronal stimulation from the site of injury/ incision and direct release of cytokines (IL1, IL6, TNFα) from macrophages and monocytes in the damaged tissues (Egdahl, 1959). There is activation of the sympathetic nervous system and release of catecholamines; an increased level of ACTH stimulating the release of glucocorticoids such as cortisol; and increased release of growth hormone and vasopressin (Ingle et al, 1947;Cochrane et al, 1981;Starnes et al, 1988;Hill, 2000). There is a decreased production of insulin, a reduced cellular response to insulin and a transient increase in glucagon (Thorell et al, 1999). Blood glucose level is elevated in proportion to the intensity of surgery and remains so for over 24 hours (Thorell et al, 1993). The net increase in catabolic hormones results in a breakdown of carbohydrate, fat and protein (Bessey et al, 1984;Shaw et al, 1987;Bessey et al, 1993). Protein (predominantly skeletal muscle but including visceral protein) is broken down for the production of energy and acute phase proteins resulting in muscle wasting and weight loss (Kinney et al, 1983;Schricker et al, 2001). There is lipolysis and mobilisation of triglycerides (Jörgen et al, 1991). The increased release of vasopressin promotes water retention through concentration of urine along with the Renin-angiotensin-aldosterone

system, which promotes the reabsorption of sodium and water from the distal tubules in the kidney. The increased release of catecholamines produces tachycardia and hypertension (Desborough, 2000).

Overall there is a mobilisation of substrate to provide energy, which is combined with a mechanism to retain salt and water to support cardiovascular haemostasis. These responses have presumably evolved to confer a survival benefit (allowing catabolism of stored body fuels and maintained blood pressure). Within modern surgical practice, however, they may be less useful and if prolonged they may have deleterious effects on the body's nutritional status and physiological reserves (Kehlet, 1997). Left unabated this surgical stress response, compounded by the effects of traditional perioperative care (starvation, fluid overload and immobilisation), can result in functional decline following major abdominal surgery. Patients undergoing technically uncomplicated procedures therefore require an indefinite period of hospital stay. Usually the key factors that necessitate this inpatient care are a requirement for parenteral analgesia, intravenous fluids or immobility.

Although advances in perioperative care have reduced the rate of surgical and anaesthetic complications, no single intervention has been able to eliminate 'medical' complications (MI, pulmonary dysfunction, renal failure, infective complications). There is an ever-increasing number high-risk and elderly patients presenting for surgery. Traditionally within surgery these groups require special consideration and individually tailored perioperative management, however, despite this they still have an increase risk of both postoperative morbidity and mortality (Giner et al, 1996;Polanczyk et al, 2001;Fazio et al, 2004). Modification of the undesirable effects

of the stress response (organ dysfunction, immobility, catabolism) may be the key to improving postoperative outcomes.

## 1.2 The Enhanced Recovery After Surgery Concept

Enhanced recovery after surgery is a clinical pathway, which combines preoperative metabolic optimisation, optimal pain relief, perioperative stress reduction with regional anaesthesia, early enteral nutrition and early mobilisation. It aims to reduce postoperative functional decline, postoperative morbidity and accelerate postoperative recovery after major abdominal surgery.

The ERAS protocol challenges both the traditional view of an inevitable perioperative stress response and the elements of traditional perioperative care which compound postoperative organ dysfunction (Fig 1.2). Many elements of the programme elements focus on postoperative pain, gastrointestinal function and mobility. These are the main elements that delay hospital discharge; therefore addressing these may allow earlier discharge from hospital.

As patients following such protocols often achieve discharge criteria earlier and require a shorter duration of hospital stay (in comparison with those following a traditional pathway) the term 'fast-track surgery' is often used interchangeably with ERAS. However, the aim of the ERAS protocol is to reduce postoperative functional decline and morbidity. In achieving these outcomes it is likely that requirement for postoperative inpatient care will also be reduced (Basse et al, 2000). Hospital stay, however, may be unrelated to rate of functional recovery especially if other obstacles to hospital discharge exist (Maessen et al, 2007). It is possible that the organisational changes associated with 'fast track surgery' i.e. targeted discharge planning and avoidance of the potentially unnecessary inpatient days towards the end of a hospital stay are being mimicked by ERAS protocols (Maessen et al, 2008).

Other markers may better reflect the attenuation of the surgical stress response. Cardiac demand (HR/ $SpO_2$) is preserved in groups undergoing colorectal surgery within an ERAS pathway but elevated in patients following a traditional care pathway. Pulmonary function ($FEV_1$, FVC, PEF) is preserved in the ERAS group but reduced in traditional care groups (Basse et al, 2002). There is also a greater preservation of muscle strength in the early and late postoperative period in patients following an ERAS protocol (Henriksen et al, 2002). This preservation of muscle strength and organ function translates into a shorter period of convalescence, an earlier resumption of physical activities (walking up stairs, house work, driving car, shopping), a reduced fatigue score by postoperative day fourteen and a greater incidence of recommencement of leisure pursuits (Jakobsen et al, 2006).

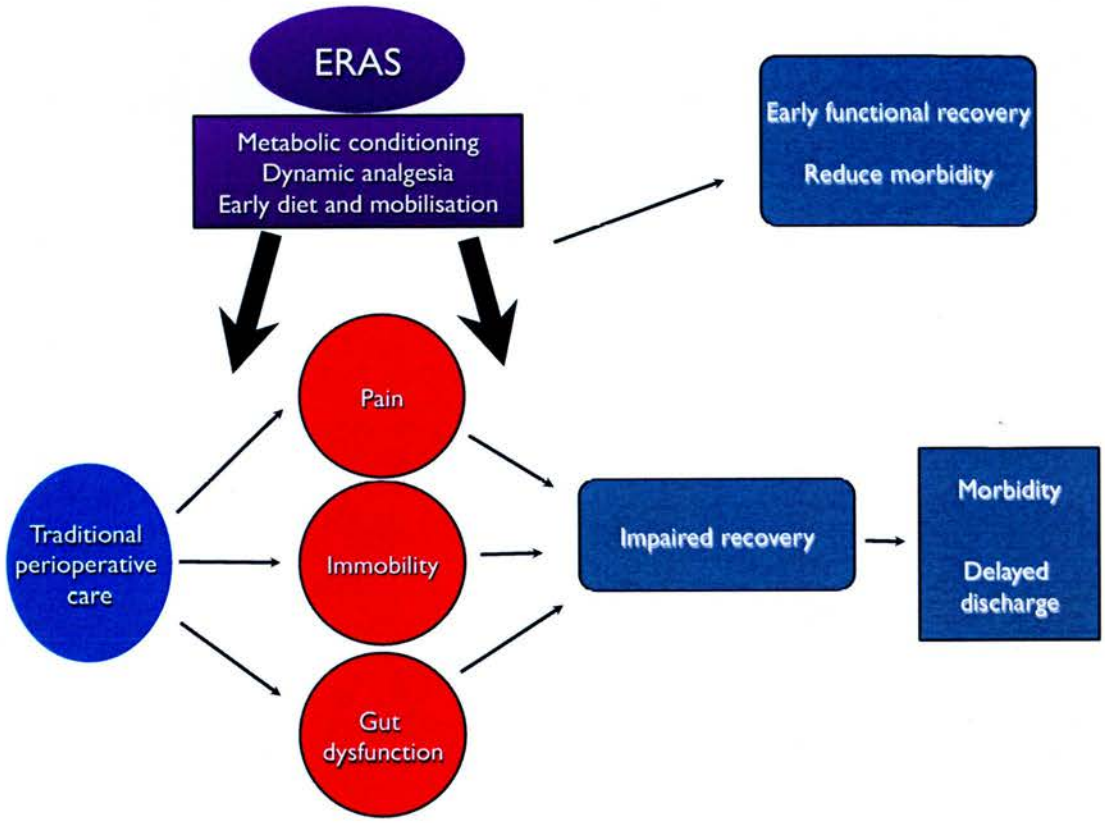
The ERAS protocol attempts to maintain the patient in as near to a physiologically and metabolically normal state (Fearon et al, 2005). The reduction in organ dysfunction associated with this regimen of care may also translate into reduced postoperative morbidity for patients undergoing colorectal resection (Wind et al, 2006). In higher risk patient groups undergoing surgery within an ERAS programme reduced postoperative morbidity will be of more benefit than reduced length of stay.

In the past two decades, the application of multimodal Enhanced Recovery After Surgery care protocols has achieved significant improvements in the outcome of a variety of surgical procedures. Such protocols are safe, effective, accelerate recovery and can reduce hospital stay following elective aortic aneurysm repair (Podore et al, 1999), oesophagectomy (Cerfolio et al, 2004) and colorectal resection (Basse et al,

2000).

These protocols, however, have not been universally adopted despite evidence to support the role of an ERAS package of care. This may be due to the fact that there are few randomised controlled trials of ERAS available and many of the existing outcome markers are subjective. The multidisciplinary nature of the protocol necessitates the participation of a large group of professionals and achieving the high rates of compliance required to achieve uniformity of patient care is difficult (Maessen et al, 2007). The increased readmission rate associated with the most dramatic results achieved in specialist centres is also undesirable (Basse et al, 2004). As there is variable evidence for the individual protocol elements many centres have chosen to implement the individual protocol elements with strong evidence rather than a more complicated care pathway.

**Fig 1.2** Target domains for ERAS



## 1.3 The components of the ERAS multimodal care pathway within colorectal surgery

The enhanced recovery protocol combines individual elements that optimise perioperative fluid balance, provide dynamic analgesia, enforce early mobilisation and encourage early oral feeding (See Figure 1.3 - 1.4). Within colorectal surgery, the introduction of the ERAS protocol has been shown to significantly reduce hospital stay from two weeks down to five days (Nygren et al, 2005;Wind et al, 2006). This can be achieved without any increase in postoperative morbidity, mortality or readmission rate (Gatt et al, 2005). A small number of studies even suggest that a two-day hospital stay may be feasible after colorectal resection, although this has been associated with a readmission rate of 11.3 – 20.1 % (Basse et al, 2000;Andersen et al, 2007).

There is a varying level of evidence to support each of the individual elements of the ERAS protocol and in many cases evidence is often extrapolated from traditional care pathways (Fearon et al, 2005). Avoiding routine mechanical bowel preparation (Guenaga et al, 2005), restricting unnecessary preoperative fasting (Brady et al, 2003) and providing preoperative oral carbohydrate loading has been shown to improve perioperative fluid balance. Restriction of postoperative intravenous fluid and sodium, judicious use of a vasopressor to treat epidural related hypotension and early return of oral fluid intake is both tolerated and has been demonstrated to further improve postoperative fluid balance (Basse et al, 2000;Holte et al, 2004). Individually these elements have been shown to reduce preoperative anxiety (Hausel et al, 2001), improve postoperative insulin sensitivity (Svanfeldt et al, 2007) and reduce

complication rate and length of stay (Noblett et al, 2006). The avoidance of long acting anaesthetic agents and pre-anaesthetic medication (Møiniche et al, 2002) reduces time to postoperative mobilisation and oral intake. The use of intraoperative epidural analgesia, achieves both analgesia and sympathetic blockade contributing to a reduction in the stress response, postoperative insulin resistance (Uchida et al, 1988) and gut paralysis (Miedema et al, 2003). Epidural analgesia in the postoperative period also provides dynamic analgesia for both open (Marret et al, 2007) and laparoscopic surgery (Senagore et al, 2003) without the side effects of sedation. Pain relief can then be maintained with step-down analgesics such as paracetamol and non-steroidal anti-inflammatory drugs.

Early postoperative feeding is promoted (Lewis et al, 2001) in the presence of a multi-modal anti-ileus package (Charoenkwan et al, 2007), even in the presence of colorectal anastomoses, and has been associated with a reduced postoperative stay (Andersen et al, 2006). The routine administration of postoperative oral nutritional supplements are of clear benefit in malnourished patients (Beattie et al, 2000) and may benefit patients that are not malnourished (Keele et al, 1997;Smedley et al, 2004). Their use in combination with preoperative carbohydrate loading and epidural analgesia has been shown to reduce catabolism and even result in nitrogen equilibrium (Soop et al, 2004). The ERAS protocol aims to facilitate early oral intake through minimising postoperative nausea, vomiting and ileus. Exposure to systemic opiates is minimised and routine intraoperative and postoperative antiemetics employed (Apfel et al, 2002). Both these measures combined with the previously mentioned avoidance of fluid overload (Nisanevich et al, 2005), epidural

analgesia (Jørgensen et al, 2000;Miedema et al, 2003;Marret et al, 2007) and early mobilisation have been shown to reduce postoperative ileus.

Minimal access surgery has been shown to reduce short-term wound morbidity, time to gastrointestinal recovery and length of hospital stay within traditional care (Tjandra et al, 2006). Its benefit is less clear within an ERAS care pathway and it has not been universally adopted (King et al, 2008). Short, transverse incisions improve rate of postoperative recovery (O'Dwyer et al, 1992) and may reduce analgesic requirement and pulmonary compromise (Brown et al, 2005).

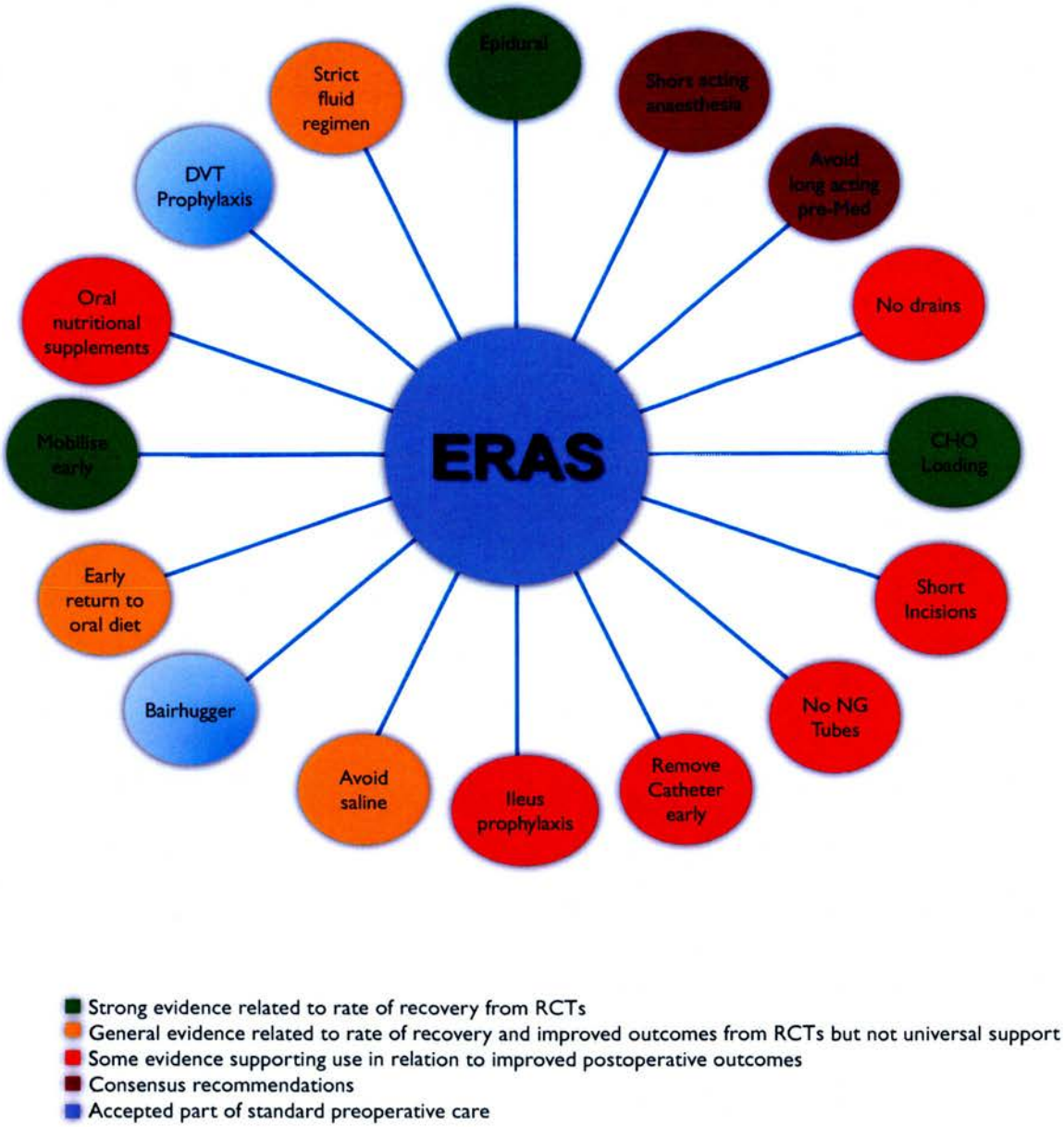
Peritoneal drains are avoided as their use does not reduce the incidence or severity of anastomotic leak (Jesus et al, 2004;Karliczek et al, 2006) and they inhibit mobilisation. Similarly urinary catheters are removed early, this may be possible within 24 hours of surgery, even with a thoracic epidural in situ (Basse et al, 2000). Mobilisation is encouraged and facilitated as protracted bed rest increases insulin resistance, muscle loss and the risk of medical complications such as thromboembolism and chest infection. Measures generally accepted within traditional care such as antibiotic prophylaxis, thromboprophylaxis, avoidance of routine nasogastric tubes and avoidance of perioperative hypothermia are also employed.

Meta-analysis of the available ERAS trials (each including at least 4 of the core ERAS elements) demonstrate that patients following such a protocol had a shorter initial hospital stay, a shorter overall hospital stay (initial stay plus readmission days) and earlier return of gut function (as marked by reduced time to first passage of flatus

and stool post surgery) in comparison to those following a traditional care pathway. There was not any significant difference in readmission rates (Wind et al, 2006).

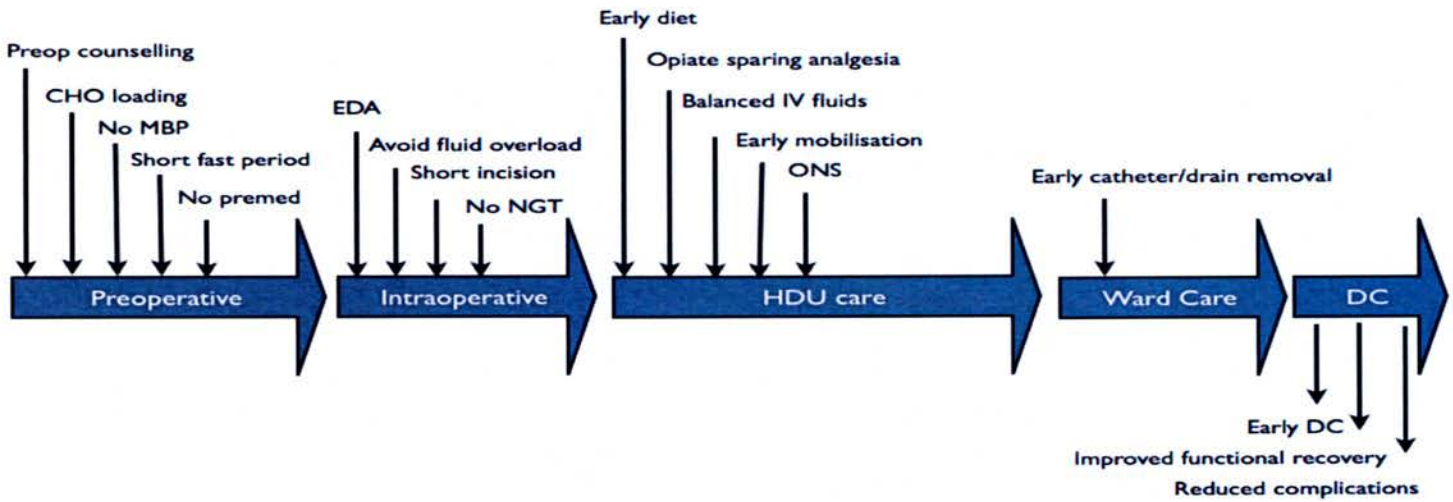
Although there is variation between the protocol elements employed in published studies, ERAS pathways reduce both postoperative length of stay and incidence of postoperative complications. Overall if such a package of care is utilised, gastrointestinal function recovers earlier, nutritional status is maintained and postoperative exercise tolerance is improved (Basse et al, 2002). However, despite these reported benefits, wide spread implementation has often been slow.

**Fig 1.3** Summary of ERAS protocol elements




Derived from figure by Fearon et al Clinical Nutrition (2005) 24, 466–477

**Fig 1.4** Timing of ERAS protocol interventions




CHO: Carbohydrate, MBP: Mechanical Bowel Preparation, EDA: Epidural anaesthesia, NGT: Nasogastric tube, ONS: Oral Nutritional Supplements, DC: discharge

## 1.4 Development of an Hepatic model of ERAS

Due to advances in liver surgery, long term survival following hepatic resection has improved dramatically. Within a traditional perioperative care pathway postoperative recovery following hepatic resection is relatively predictable especially in relation to perioperative morbidity and mortality. For simple hepatic resection published median length of hospital stay ranges from 8-14 days (Belghiti et al, 2000;Jarnagin et al, 2002;Dimick et al, 2004). Ten year survival for resection of colorectal metastases may be as high as 33% and the operative mortality as low as 1% (Memon et al, 2001).

Patients undergoing hepatic surgery are subject to a similar perioperative course as those undergoing bowel resection, therefore the stress response should be equivalent. The postoperative recovery will also be subject to the same delays from medium term sequelae: pain, poor appetite and immobility. However, following liver resection there will be no gastrointestinal anastomosis or disruption to the gastrointestinal tract. It is feasible that a modified colorectal ERAS pathway may be applied to liver surgery and due to the predictable nature of postoperative recovery may have a higher rate of protocol compliance (Maessen et al, 2007). As many of the existing individual protocol elements of the ERAS programme are extrapolated from traditional care (Fearon et al, 2005) this model of ERAS perioperative care for patients undergoing liver resection would serve as an ideal model in which to evaluate individual elements of the protocol such as early feeding and gastrointestinal stimulation and provide evidence that could be extrapolated to other surgical specialties.

## 1.5 Acceptance of the Enhanced Recovery After Surgery concept

Traditionally it has been accepted that major abdominal surgery is followed by a prolonged period of postoperative recovery. Postoperative length of hospital stay for patients undergoing colorectal resection has been quoted as 10-12 days (Bokey et al, 1995;Schoetz et al, 1997) with a complication rate of 15 – 48 % (Bokey et al, 1995;Basse et al, 2000). Moreover, certain elements routinely employed in traditional perioperative care have been shown to have a negative effect postoperative recovery. Drains and catheters reduce mobility (Jesus et al, 2004;Karliczek et al, 2006) and both prolonged fasting and sodium rich intravenous fluids (Lobo et al, 2002) delay gastrointestinal recovery. The ERAS programme was devised to address these particular issues (Fearon et al, 2005) and its adoption has resulted in an improved rate of recovery following colorectal surgery. Certain specialist centres achieving a length of hospital stay as low as 2 - 3 days (Kehlet et al, 1999;Andersen et al, 2007). The ERAS protocol has been tailored to other areas such as oesophagectomy (Cerfolio et al, 2004;Jiang et al, 2009), aneurysm repair (Podore et al, 1999;Murphy et al, 2007) and gynaecological surgery (Moller et al, 2001;Ottesen et al, 2002) with a similar reduction in length of hospital stay and morbidity. It may therefore be possible to apply this system of care to most major surgical procedures and its use in hepatic surgery will be explored within this thesis.

Despite the evidence supporting the implementation of an Enhanced Recovery After Surgery most of the existing data is subject to the similar limitations. These limitations may go some way to explain why universal uptake of the ERAS protocol has been slow.

The majority of studies examining the role of an ERAS programme compare the outcomes achieved within an ERAS group with either a retrospective group of patients following a traditional care pathway, patients undergoing care in another institution (Hjort Jakobsen et al, 2004) or even care within another country (Nygren et al, 2005). Moreover, only a small number of trials adequately randomise patients to ERAS versus a traditional care (Anderson et al, 2003;Gatt et al, 2005).

Blinding is an important part of the methodology in randomised controlled trials, however, both blinding and randomisation are difficult to perform in ERAS trials. Attempts that have been made to decrease bias include the introduction of objective discharge criteria (Gatt et al, 2005). Other elements are more difficult to blind from the subject and the assessor. For elements such as reduced preoperative fasting, CHO/fluid loading, epidural use, early postoperative mobilisation, early feeding and avoidance of drains and catheters it is simply not possible to blind the subject. Preoperative counselling is a significant part of the ERAS protocol. This is seen to empower patients and give them ownership of their recovery and inform them about the benefits of early postoperative mobilisation and diet early. Medical staff are also part of this perioperative journey. Many of the elements of the ERAS protocol require both motivated patients and hospital staff and it is clear that improved protocol compliance may promote further improvements in postoperative outcomes (Maessen et al, 2007). As the key to further improvements appears to be the intervention of hospital staff and compliance of patients it would appear that efforts to enforce blinding might hinder further improvements.

Elements of the ERAS programme of care may be adopted on an element-to-element basis depending on available evidence. Perioperative thoracic epidural analgesia has become almost standard practice, carbohydrate loading is being readily adopted and there is increased emphasis on early postoperative mobilisation and feeding. The individual elements employed within ERAS are based on the best available evidence. Although such a perioperative care strategy may not incorporate all of the elements of the ERAS programme or indeed may not mobilise or feed patients as it does represent an evolution towards the ERAS protocol of care.

Within the multimodal ERAS programme of care much of the evidence for the individual elements is taken in isolation from traditional care pathways, consensus review or simply accepted standard care (as described in Sections 1.3,1.4). Little evidence is available concerning the importance of each element when considered within the context of an enhanced recovery pathway. For this reason there may be resistance to adopting the entire ERAS programme of care, which may be regarded as complicated and labour intensive, in favour of adopting individual elements such as perioperative epidural analgesia and preoperative carbohydrate loading for which strong supporting evidence exists.

Moreover, specific elements such as minimal access surgery have been associated with improved short-term postoperative outcomes, shorter hospital stay, reduced morbidity and postoperative pain when compared with open surgery within traditional care (Abraham et al, 2004). Minimal access surgery is associated with early mobilisation and oral diet without the intervention of an ERAS programme (Tjandra et al, 2006). Within an ERAS programme of care no further improvement has been identified (MacKay et al, 2007), however, there may be increased patient satisfaction

with laparoscopy and an earlier return to activities such as driving or hobbies (King et al, 2008).

Furthermore, the readmission rate of 20 - 25 % reported for the seminal fast-track programme in Denmark would be unacceptable in many centres (Basse et al, 2000). Although more recent papers with a less aggressive planned length of stay have been associated with a much lower readmission rate (Andersen et al, 2007) the perception of increased readmission with early discharge persists.

ERAS programmes are often considered a strategy for younger and fitter patients, specifically targeting early discharge. Therefore not all patients may be considered as eligible for such a programme, creating a two-tier system. Arguably the elderly, those with comorbidity and the undernourished may have as much if not more to gain in the form of reduced postoperative morbidity, this is discussed further in this thesis.

Traditionally targeted pre-optimisation of patients with high levels of comorbidity, the elderly or those with preoperative malnutrition has been employed. Where the clinical situation allows, further optimisation of the patients physiology on the form of blood pressure, heart failure and diabetic management, correction of anaemia and improvement of nutritional status are all associated with improved outcomes. More recently cardiopulmonary exercise testing is becoming more prevalent (Older et al, 2000;Older et al, 2004). This tailored approach to preoperative care may not be a well recognised part of most ERAS programmes, however, where appropriate relevant modifiable risk factors should be addressed in the preoperative period. The success of many perioperative interventions is evaluated against patient comorbidity and indeed

many ERAS programmes compare predicted outcome calculated from P-POSSUM scores or group patients according to American Society of Anesthesiologists grade. These, however, often overestimate postoperative morbidity or mortality. The ERAS programme itself me be considered a preoperative strategy, as carbohydrate is one of its most significant components along with preoperative use of epidural analgesia. Moreover, many of the postoperative elements of the ERAS protocol could be considered as outcomes of recovery in themselves

## 1.6 Issues with ERAS protocol compliance

Although compliance is not universally reported within ERAS trials, it will be significant when an ERAS cohort is being compared with a retrospective cohort of patients. It has been demonstrated that a reduced length of hospital stay may be explained by a policy targeting early discharge rather than any real improvement in rate of recovery (Maessen et al, 2008). Within papers that do report protocol compliance there appears to be a similar pattern of greater compliance with preoperative and intraoperative elements and not postoperative elements (Gatt et al, 2005;Maessen et al, 2007).

Maessen and colleagues also suggest a relationship between compliance with postoperative elements of the care protocol and shortened hospital stay (Maessen et al, 2007). Postoperative variables often overlap as both markers of protocol compliance and markers of postoperative recovery. It is therefore difficult to draw conclusions, as multivariate analysis will be confounded. This problem highlights the difficulties of establishing objective outcomes on which to evaluate the success of ERAS programmes. It is important that the introduction of an ERAS protocol is accompanied by appropriate audit to assess the success of the programme, to highlight areas where further development may be required and to specify the most significant elements of the protocol (Wind et al, 2006). Within the randomised controlled trial presented in this thesis, compliance with elements of the ERAS protocol was audited prospectively.

## 1.7 Limitations of existing clinical outcomes

In achieving an improved rate of recovery, it may be possible to reduce the requirement for inpatient care and facilitate early discharge from hospital. Within the ERAS protocol, however, the reduced requirement for inpatient care should be a side effect of the faster functional recovery. Length of hospital stay (LOS) is often quoted as a measure of the success of enhanced recovery programmes, however, it is also used as an index of hospital efficiency. Outwith the development and implementation of ERAS programmes other protocols and guidelines have been introduced to regulate inefficient use of services. Scheduled discharge planning and increased use of primary health care facilities are aimed specifically at reducing the length of postoperative hospital stay, often targeting the lower intensity days towards the end of a hospital admission when medical discharge may be appropriate. There are inherent flaws in using length of postoperative hospital stay as an outcome. It is not necessarily an objective measure of recovery. Moreover, a shorter recovery period may not automatically result in a shorter length of hospital stay.

Initial evaluation of the length of hospital stay for patients managed within an ERAS programme revealed that up to 70% of patients were not being discharged on the day that they achieved all of the discharge criteria (No requirement for intravenous fluids, tolerance of solid food, good pain control on oral analgesics and mobilisation to preoperative level) (Maessen et al, 2007). Follow-up studies show that up to 87% of patients managed within an ERAS programme had discharge delayed beyond the point in time when they met discharge criteria. A similar delay was identified in 90 % of patients managed within a traditional care pathway. The median delay to discharge was 1 day for the ERAS group and 2 days for the traditional care

group ($p<0.01$) (Maessen et al, 2008). It is clear that the effect of a shorter recovery period on length of stay is frustrated by additional days in hospital beyond the patients achieving discharge criteria. Although in the study by Maessen and co-workers (2008) there was not any significant difference between the ERAS group and the Traditional Care (TC) group with regard to the number of patients who had a delayed discharge, there was a significant difference in the median number of delayed days to discharge in each group. It may be that reduction in the median length of delayed discharge beyond when the patient achieves discharge criteria reflects a change in the attitudes of the medical and nursing staff rather than a true improvement in the rate of recovery.

Traditionally, factors such as patient age, severity of disease, pre-existing comorbidity, postoperative complications and social circumstances along with availability of beds and hospital discharge policies (Seymour et al, 1982;Epstein et al, 1988;van Doorslaer et al, 1989;Burns et al, 1991;Maessen et al, 2007) have all been shown to affect length of hospital stay. Postoperative complications specifically have been shown to have a strong adverse influence on length of stay (Maessen et al, 2007). Familiarity with the ERAS protocol, previous experience with an ERAS programme and elements associated with restoration of food intake were associated with early recovery and discharge from hospital. However, it has not been possible to demonstrate which other protocol elements have an independent influence on outcome.

Protocols that have targeted a particularly short length of inpatient stay have been associated with higher readmission rates (15 – 27 % compared with 2 – 16 % within

traditional care) (Basse et al, 2000). When a three day postoperative stay was planned rather than two days following elective colonic resection, readmission rate was reduced from 20.1 – 11.3 % (Andersen et al, 2007). The latter study highlighted that although the number of readmissions related to surgical complications remained unchanged, when the length of stay was increased to 3 days there were fewer readmissions for observation or social reasons.

There is an expected incidence of complications following major colorectal surgery and there must be appropriate preadmission counselling and a clear pathway for prompt and safe readmission of the 1 – 3 % of patients who may experience an anastomotic leak (Fearon et al, 2005). If this pathway is not available then safe discharge from hospital cannot take place and early discharge from hospital is not an appropriate target. This is also important for patient satisfaction, as patients themselves do not always want to be discharged from hospital early (Basse et al, 2005).

It is expected that postoperative complications, such as infection rate, will be beneficially modulated by a relatively stress free perioperative care pathway which promotes improved immune function. However, using this as an outcome marker is difficult as shorter lengths of hospital stay may result in many of the minor infective complications being diagnosed and treated in the community.

Time to first passage of flatus or passage of stool post surgery is traditionally used to guide reintroduction of oral diet and has been employed in several papers as a surrogate marker of return of gastrointestinal function (Basse et al, 2000). However,

time to passage of stool may not be an appropriate measure of upper gastrointestinal function. Oral intake or the ability to assimilate nutrients in the early postoperative phase may be tolerated days prior to the passage of flatus or stool (Catchpole, 1989). Following major abdominal surgery, feeding in the first 24 hours has been shown to be safe, even following colorectal anastomosis. Oral intake of food is associated with a reduced length of stay and lower mortality rate (Andersen et al, 2006). However, there is an increased risk of bloating, nausea and vomiting with early feeding. One of the aims of the ERAS programme is to hasten recovery of gastrointestinal function, thereby promoting assimilation of calories and minimising catabolism in the early postoperative period.

An appropriate objective marker of postoperative gastrointestinal recovery is of great interest when examining this key domain of the recovery protocol. Currently there is no universally applied objective measure of gastrointestinal function in the postoperative period and often surrogate markers such as time to first passage of flatus/ stool or calorie intake are used. Discontinuation of intravenous fluids, tolerance of oral fluids or oral diet, time out of bed and mobilisation have also been used as markers of recovery, however, many of these outcomes are in themselves protocol elements and therefore may simply mark compliance. An objective measure of gastrointestinal recovery may be one of the most robust milestones of overall functional recovery.

## 1.8 The role of nutritional conditioning/support within ERAS

The role of preoperative metabolic conditioning with an orally administered 12.5% carbohydrate solution has become a significant part of most ERAS programmes (Svanfeldt et al, 2007). The administration of such a carbohydrate-rich drink stimulates the release of insulin and mimics the effect of a mixed meal (McMahon et al, 1989). As a clear fluid, such a carbohydrate rich drink, can be administered safely up to two hours prior to anaesthetic induction (Nygren et al, 1995) in keeping with modern preoperative fasting guidelines (Søreide et al, 2006). Fluid and carbohydrate loading prior to surgery assists in the optimal maintenance of fluid balance (Lobo et al, 2006) and reduces preoperative thirst and anxiety before elective surgery (Hausel et al, 2001). In the early postoperative period a reduction in nausea has also been demonstrated following laparoscopic cholecystectomy (Hausel et al, 2005).

Preoperative carbohydrate loading reduces postoperative insulin resistance (Nygren et al, 1998) due to an increase in glucose disposal in peripheral tissue and improved oxidative metabolism in the early postoperative phase (Soop et al, 2001). This effect persists up to three days post surgery and can result in a measurable reduction in nitrogen loss (Soop et al, 2004). When used as part of an ERAS programme of care postoperative enteral feeding can be provided without hyperglycaemia and achieve nitrogen balance (Soop et al, 2004). Preoperative carbohydrate loading may also attenuate postoperative loss of muscle mass (Yuill et al, 2005). In colorectal surgery its use is associated with a reduced duration of postoperative stay (Noblett et al, 2006).

It is proposed that the addition of other nutrients in combination with carbohydrate may promote further benefits in postoperative recovery. However, any novel preparation must have a rapid gastric emptying profile to be administered safely prior to surgery. This thesis explores the gastric emptying profile of such a novel drink containing glutamine and antioxidants in combination with carbohydrate to assess its suitability as a preoperative metabolic conditioning regimen.

In the period following major abdominal surgery weight loss is known to continue up to eight weeks beyond surgery. Use of nutritional supplements in malnourished patients, (defined as those with a BMI </= 20 $kg/m^2$, anthropomorphic measurements </= $15^{th}$ percentile on admission or initiation of diet postoperatively and/ or weight loss of 5% or more during the perioperative period), have been shown to reduce the period of weight loss to 4 weeks and significantly reduce the overall amount of weight loss along with improving quality of life and morbidity (Beattie et al, 2000).

In unselected patients undergoing moderate to major gastrointestinal surgery administration of oral nutritional supplements ad libitum within the early postoperative period results in a significantly increased overall calorie intake. Not only as a consequence of the energy intake form the supplements but due to more of the ward diet being consumed (Rana et al, 1992). Those receiving oral nutritional supplements lose less weight in the postoperative period (Keele et al, 1997) or may even maintain their preoperative weight (Rana et al, 1992). They also have a smaller decrease in grip strength and lower incidence of wound infection. Patients receiving ONS who have lost weight in the perioperative period appear to return to preoperative

weight earlier, report lower levels of fatigue (Keele et al, 1997) and suffer fewer major complications (Lawson et al, 2003).

It has been suggested that perioperative oral nutritional supplementation started before hospital admission for lower gastrointestinal tract surgery diminishes the degree of weight loss and incidence of minor complications (Smedley et al, 2004) although some studies disagree that any benefit exists for patients that are otherwise well nourished (MacFie et al, 2000). Within an elderly population undergoing orthopaedic surgery the effectiveness of oral supplementation is dependent on compliance (Bruce et al, 2003) and within the normally nourished or mildly malnourished patient group benefit may be restricted to patients suffering postoperative complications or a prolonged hospital stay (Botella-Carretero et al, 2008).

Within traditional perioperative care enterally administered perioperative immunonutrition has been shown to reduce postoperative infections rate and length of hospital stay (Braga et al, 1999). Nasojejunal feeding within an ERAS protocol is associated with minimal postoperative insulin resistance and nitrogen loss (Soop et al, 2004).

The ERAS programme of care promotes the combination of preoperative oral carbohydrate loading with both early return of diet and oral supplementation. Although there is clear evidence supporting the benefits of the ERAS programme of care as a package (Wind et al, 2006) the contribution gained from combining

preoperative oral carbohydrate loading and postoperative ONS has not been fully examined.

## 1.9 The role of laxation/optimised gastrointestinal function within ERAS

Major abdominal surgery is associated with a period of gastrointestinal dysfunction or postoperative ileus that may persist up to five days beyond surgery (Miedema et al, 2003). This is characterised by bowel distension, absence of bowel sounds and a delayed passage of flatus and stool. It can delay resumption of oral diet, mobilisation and discharge from hospital and contribute to postoperative pain and complications. Traditionally, postoperative ileus has been accepted as an unavoidable consequence of abdominal surgery, however, the benefit of such a physiological response is unclear. Although postoperative ileus is particularly related to the degree of intraoperative bowel handling (Kalff et al, 1998), the persistence of postoperative gastrointestinal dysfunction and ileus is multifactorial. Not all parts of the gastrointestinal tract are equally affected. It is believed that the small intestine recovers within the first 24 hours, the stomach within 48 hours and the colon within 72 hours (Catchpole, 1989;Holte et al, 2000). Clinically ileus and its resolution are not well defined.

Within the ERAS programme of care the multifactorial approach to treating postoperative gastrointestinal dysfunction combines limiting the factors that contribute to ileus, such as systemic opiates and utilising factors that promote early recovery of gastrointestinal function such as mid-thoracic epidural analgesia or balanced intravenous fluid therapy (Luckey et al, 2003). This multimodal approach within the ERAS programme has been shown to reduce the duration of postoperative gastrointestinal dysfunction (Wind et al, 2006).

Laxatives, although commonly used in the postoperative period, are not administered routinely and only a small number of studies have examined the effectiveness of their routine administration. Magnesium salts combined with bisacodyl suppositories administered to a series of twenty patients undergoing gynaecological surgery promoted a faster gastrointestinal recovery and earlier discharge from hospital (Fanning et al, 1999;Hansen et al, 2007). Magnesium salts have also been employed within an ERAS protocol of care for patients undergoing colorectal surgery, which as a package of care has facilitated shorter time to first passage of stool and earlier discharge from hospital (Basse et al, 2004;Nygren et al, 2005), however, the specific impact of postoperative laxation, within these ERAS protocols, is not clear. Bisacodyl has also been shown in a randomised controlled trial to promote earlier passage of flatus and stool and tolerance of oral diet following colorectal resection (Zingg et al, 2008).

Sham feeding has been shown to promote a shorter time to passage of flatus and stool but not a shorter hospital stay or reduced complications (Parnaby et al, 2009). However, since reintroduction of diet following colorectal surgery is both tolerated and safe (Lewis et al, 2001) the role of sham feeding is less clear. Although several studies have demonstrated early tolerance of food, return to full diet and even earlier recovery of bowel sounds this did not always equate to a cessation of postoperative ileus (Reissman et al, 1995;Feo et al, 2004;Charoenkwan et al, 2007). Some studies have suggested that early diet itself results in an earlier recovery of gastrointestinal function and discharge from hospital (Stewart et al, 1998). Within a multimodal programme of interventions, elements such as early mobilisation have been shown to be associated with early recovery of gastrointestinal function (Henriksen et al, 2002).

Although other pharmacological agents have been suggested to be effective, evidence is limited and insufficient to allow recommendation of a particular agent. Alvimopan (a μ-receptor antagonist) may have a beneficial role (Traut et al, 2008) but has not been widely adopted.

It is clear that minimising the period of postoperative gastrointestinal dysfunction will allow early ingestion of food and improve rate of recovery. Further improvements in the effect of the ERAS protocol may rely specifically on improving the rate of gastrointestinal recovery. Evidence of a specific benefit from routine postoperative laxation, within an ERAS programme, is limited. This thesis examines the use of routine postoperative magnesium hydroxide within an ERAS protocol of care following major abdominal surgery and any potential interaction of such laxation with preoperative metabolic conditioning and postoperative oral nutritional supplement administration.

## 1.10 Further Development of the ERAS model

Although many of the elements of the ERAS programme have been validated in meta-analysis or randomised controlled trials, adoption of these standards is still varied. This may be due to longstanding surgical traditions regarding elements such as preoperative fasting and early postoperative feeding. Some of the elements of the ERAS programme (minimal use of mechanical bowel preparation, drains and nasogastric tubes along, improved perioperative nutrition and early mobilisation) have been employed to a varying degree in different surgical units and lead to regional and international variations in practice (Nygren et al, 2005). Introduction of the ERAS protocol requires comprehensive education and audit to assess compliance (Fearon et al, 2005).

The protocol itself is subject to refinement as further evidence becomes available. Currently many of the elements are based on evidence gained within traditional care. Therefore although the ERAS package of care overall has been shown to be of benefit (Wind et al, 2006), the individual contributions of each protocol elements remains unclear.

The outcomes used to evaluate the success of the ERAS programme will have to evolve. It is clear that the implementation of the ERAS programme has reduced the requirement for hospital stay (Wind et al, 2006). However, in future studies, length of hospital stay may not be sensitive enough to assess the efficacy of further subtle changes to the programme (Maessen et al, 2007;Maessen et al, 2008). The application of discharge criteria and achievement of functional recovery have been used as a more

objective outcome, however, novel markers of postoperative mobility, gastrointestinal function or assimilation of calories may provide a better measure of recovery.

The reduction in postoperative morbidity is the most desirable outcome of the ERAS protocol especially in higher risk groups. Currently, careful screening and focussed care has been shown to be effective in reducing adverse outcomes in high-risk subgroups of patients, however, it is difficult to screen patients adequately (Murphy et al, 2006). Debate exists over the most effective method of screening and in many busy surgical units screening is simply not performed. It is proposed within this thesis that a stress free and nutritionally aware ERAS programme will provide better outcomes for all patients, including those traditionally at higher risk, rather than screening patients and providing focussed care only to those at risk. It is possible that the improved postoperative outcomes achieved within an ERAS programme will be applicable to all patients.

It is suggested that improving postoperative compliance with the ERAS protocol may provide greater improvements but will also be more challenging. Postoperative routines are more difficult to influence and may require a greater structural change along with education of the junior medical and nursing staff that frequently rotate through other wards and specialties.

The original positive results from the Enhanced recovery publications need to be supported by further robust randomised clinical trials. It may be more useful to investigate the specific impact of individual elements within the overall ERAS protocol, this is explored further in the present thesis.

## SECTION C. THE ERAS MODEL OF PERIOPERATIVE CARE

## *Chapter 2. The colorectal model: Results from the ERAS international collaboration. What outcomes can be achieved and which patient subgroups benefit?*

### 2.1 Background

This chapter examines postoperative outcomes for patients undergoing colorectal resection within an ERAS programme of care in four different European centres. Specifically the outcomes for patients traditionally considered high risk. Patients were grouped according to preoperative BMI (WHO categories) as an indicator of preoperative nutritional status and given the elderly nature of the overall population a BMI < 20kg / $m^2$ was considered as indicating risk of undernutrition. Patients were also grouped according to age and comorbidity with those ≥ 80 years old considered elderly and patients with an ASA (3-4) considered to have major comorbidity. The aim of this chapter was to establish if these higher-risk patients can also achieve the improved postoperative outcomes associated with an ERAS programme of care. This would remove the requirement for patient screening and tailored perioperative management of higher-risk patients.

Patients undergoing major abdominal surgery can be at increased risk of delayed recovery, morbidity and mortality due to a variety of factors including age, undernutrition and comorbidity. This increased risk may be due to the combined effects of tissue wasting, impaired immune function, impaired healing and organ dysfunction (Arora et al, 1982;Giner et al, 1996). The links between advanced age or poor nutritional status and adverse surgical outcome have long been recognised (Studley, 1936;Ergina et al, 1993;Hill, 1994). Although it may be argued

that modern surgery with prophylactic antibiotics, better analgesia, improved suture materials and high dependency postoperative care might avoid such adverse outcomes, recent studies involving traditional perioperative care show that a similar relationship still exists (Polanczyk et al, 2001;Hamel et al, 2005). Indeed, a recent study showed that in-hospital mortality for colorectal patients over 85 years of age was nine-times as high as that for those aged 65 and under (Fazio et al, 2004).

Although recent evidence suggests an epidemic of obesity (World Health Organisation, 2000), a significant proportion of the surgical population remain undernourished and potentially at increased risk (Beattie et al, 2000). Likewise, it is evident that the general population is getting older. In the USA life expectancy is seven years for the average 80-year-old man and nine years for the average 80-year-old women (Manton et al, 1995). In such elderly patients, increased morbidity / mortality following surgery is thought to result from a lack of organ function / reserve to sustain the patient in the event of complications (Ergina et al, 1993). However, it is often difficult to discriminate between the risks attributable primarily to one factor by itself (e.g. age) versus the compounding effects of other co-variables (e.g. increased comorbidity with old age).

Enhanced Recovery After Surgery (ERAS) is based on reducing the surgical stress response and supporting basic body functions by the use of optimised analgesia, early mobilisation and early return to normal food / diet (Fearon et al, 2005;Kehlet, 2008). These interventions have been shown to improve postoperative outcomes (Wind et al, 2006;Khoo et al, 2007;Varadhan et al, 2010). The elderly appear to be at particular risk of mortality once a postoperative complication has developed (Hamel et al,

2005). It is therefore of interest that systematic analysis of enhanced recovery has suggested that ERAS may favourably influence postoperative morbidity (Wind et al, 2006;Varadhan et al, 2010) and therefore might be a particularly useful prophylactic measure for patients at risk (e.g. the elderly).

This chapter presents a study looking at the feasibility, efficacy and safety of an ERAS protocol for open, elective colorectal surgery. Observed morbidity and mortality rates have been compared with the predicted rates based on Portsmouth-Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (P-POSSUM) scoring (Prytherch et al, 1998). In addition the prognostic value of BMI, age, ASA grade, malignancy status, gender and operation type were investigated

## 2.2 Patients and methods

Between March 2002 and December 2005 patients aged 18 – 94 years undergoing elective open colorectal surgery with formation of an anastomosis (above the peritoneal reflection) were included. The upper limit of the rectum was defined as level with the sacral promontory. Patients with rectal cancer were included if the tumour was in the upper 1/3 of the rectum and allowed anastomosis in the middle 1/3 of the rectum (at or about the level of the peritoneal reflection). Patients requiring total mesorectal excision were excluded. Most sigmoid and all rectosigmoid and upper rectal tumours underwent formal anterior resection with high ligation of the vessels and takedown of the splenic flexure. Patients with benign or malignant pathology and with an American Society of Anaesthesiology (ASA) grade of 1-4 were included in the study. Four Departments of Surgery in Northern Europe (University Hospital, Maastricht, The Netherlands; University Hospital Northern Norway, Tromsø, Norway; Karolinska Institute at Ersta Hospital, Stockholm, Sweden; The Western General Hospital, Edinburgh, UK) participated for a minimum of 12 months. Ethical approval and informed written consent was obtained from all patients in centres where de-identification of data did not provide dispensation of this obligation.

All patients followed an ERAS protocol based on continuous thoracic epidural anaesthesia / analgesia, early mobilisation and diet and nutritional supplements as published previously (Fearon et al, 2005) (Table 2.1). Mechanical bowel preparation was not used routinely but was applied mainly before left-sided or anterior resections when employed. Compliance was audited prospectively.

**Table 2.1 Enhanced Recovery After Surgery Guidelines for patients undergoing colorectal resection**

| Time period | Guideline |
|---|---|
| **Prior to admission** | **Preoperative counselling** (Egbert et al, 1964;Disbrow et al, 1993;Kiecolt-Glaser et al, 1998;Halaszynski et al, 2004;Forster et al, 2005) |
| **Day before surgery** | **Normal diet until midnight** (Brady et al, 2003)<br>**No preanaesthetic medication** (Smith et al, 2003)<br>**Selective use of mechanical bowel preparation** (Wille-Jorgensen et al, 2003;Slim et al, 2004;Contant et al, 2007;Jung et al, 2007;Guenaga et al, 2009) |
| **Day of surgery** | **Carbohydrate drink 2 hours before surgery** (Hausel et al, 2001;Yuill et al, 2005;Noblett et al, 2006;Svanfeldt et al, 2007)<br>**Mid-thoracic epidural analgesia (local anaesthetic and low-dose opioid)** (Uchida et al, 1988;Liu et al, 1995;Jørgensen et al, 2000;Block et al, 2003;Miedema et al, 2003)<br>**Short acting anaesthetic agent**<br>**Minimal incision length/ transverse incision** (O'Dwyer et al, 1992)<br>**No nasogastric drainage** (Cheatham et al, 1995;Nelson et al, 2007)<br>**Intraoperative body warming device** (Kurz et al, 1996;Schmied et al, 1996;Frank et al, 1997;Scott et al, 2006;Wong et al, 2007)<br>**Avoidance if excessive IV fluids (intraoperative and peroperative)** (Lobo et al, 2002;Brandstrup et al, 2003;Tambyraja et al, 2004;Nisanevich et al, 2005;Rahbari et al, 2009)<br>**No routine drainage of the peritoneal cavity** (Jesus et al, 2004;Karliczek et al, 2006)<br>**Early Resumption of oral diet** (Lewis et al, 2001;Andersen et al, 2006;Charoenkwan et al, 2007;Han-Geurts et al, 2007)<br>**ONS ad libatum** (Keele et al, 1997;Beattie et al, 2000;Smedley et al, 2004) |
| **Postop day 1** | **Early mobilisation** (Kehlet et al, 2002)<br>**Early discontinuation of IV fluids** (Basse et al, 2000)<br>**Continuation of epidural/ opiate sparing analgesia** (Marret et al, 2007) |
| **Postop day 3** | **Stop epidural/ stepdown analgesia**<br>**Removal of urinary catheter** |

***Measurements***

In all centres data were collected prospectively, on a computerised database as described previously (Maessen et al, 2007). Data included patient demographics (including preoperative BMI), surgical procedures and postoperative outcomes (including time to achieve targeted mobility, total length of hospital stay, complications and 30 day mortality). Follow-up for morbidity and mortality was verified either during the primary admission, by telephone contact at 30 days or at the subsequent outpatient clinic visits.

Time to achieve targeted mobilisation was defined as the number of days after surgery until the patient was out of bed >6 hours / day and at the same level of independence for activities of daily living as prior to surgery. Total length of stay was defined as the number of nights spent in hospital after surgery, including nights after readmission within 30 days after surgery. To define the influence of complications on postoperative recovery and hospital stay, all adverse events in the postoperative period were recorded prospectively as described previously (Nygren et al, 2005). A patient's postoperative course was considered complicated if any complication by accepted standard definitions occurred (Lang et al, 2001;Basse et al, 2004).

Patients were grouped according to preoperative BMI (World Health Organisation categories) (World Health Organisation, 2000), as an indicator of preoperative nutritional status. Given the elderly nature of the overall population a BMI below 20 $kg/m^2$ was considered to indicate a risk of undernutrition. Patients were also grouped according to age (less than 80 years, 80 or more years) and grade (low, 1-2; high, 3-4).

***Morbidity and Mortality analysis***

Predicted [expected (E)] morbidity and mortality were based on P-POSSUM scoring (Prytherch et al, 1998) with the observed (O) morbidity and mortality recorded up to 30 days post surgery. Results were expressed as O:E ratios. Missing values (less than 5 percent of all variables) for P-POSSUM were assumed to be normal.

***Statistical analysis***

SPSS (version 16 for Mac; SPSS Inc. Chicago, Illinois, USA) was utilised to analyse the data. Data were collected prospectively to assess the efficacy of an Enhanced Recovery After Surgery programme and included all patients undergoing elective colorectal resection with an ASA grade 1-4. No specific sample size calculation was undertaken.

The dataset was analysed using time to achieve mobilisation, total length of hospital stay, complication rates and 30d mortality as the main outcome variables. Factors possibly influencing these variables included: gender, age (less than 80 years or 80 or more years), type of surgery (colonic, rectal), presence of malignancy, BMI (less than 20 or at least 20 $kg/m^2$) and comorbidity (ASA 1-2, 3-4). Univariate analysis was initially undertaken to assess any relationship between all the elements described above and the defined outcome variables. Comparisons were made using Chi-squared test or Fisher's exact test where appropriate for all categorical variables and Mann-Whitney U test for continuous variables. Multivariate analysis, using binary logistic regression for categorical variables and linear regression of log transformed

continuous variables, was then performed for all variables with a significant or near significant difference ($p < 0.15$) demonstrated in univariate analysis. In multivariate analysis non-significant factors were excluded sequentially and the model rerun. $P < 0.05$ were considered statistically significant.

## 2.3 Results

A total of one thousand and thirty five patients followed the ERAS protocol. Compliance with preoperative and intraoperative elements of the protocol was high (87.5 % patients received preoperative counselling and instruction, 63.4 % patients completed carbohydrate loading and 87.6 % patients received epidural analgesia / anaesthesia). Protocol compliance in the postoperative phase was lower (IV fluids discontinued on the day after surgery in 44.3 %, 39.2 % were out of bed on the day of surgery and 61.4 % resumed full diet on the day after surgery). Overall demographics and outcomes are shown in Table 2.1. The male to female ratio was 1:1.1 and 68.6 % were treated for malignant disease. There were 724 colonic and 311 rectal resections. Some 7.9 % of patients had a BMI below 20 kg / $m^2$, 18.7 % were aged 80 years or more and 20.6 % had an ASA grade of 3-4.

The overall median time to achieve targeted mobilisation was 3 days and total length of hospital stay was 6 days. The overall readmission rate was 8.6 %, reoperation rate 7.4 % and anastomotic leak rate 5.1 %. The morbidity rate for the whole group was significantly lower than that predicted by P-POSSUM [observed: expected (O:E) 0.68 ($p < 0.001$], and 30-day mortality was not significantly different from the predicted value [O:E 0.68 ($p = 0.212$)]. Patients undergoing rectal resection had a longer hospital stay, a higher overall complication rate and were readmitted more frequently than those having colonic surgery. In contrast, observed: expected morbidity and mortality tended to be higher in the colonic resection group.

**Table 2.1 Overall Demographics and Outcomes: 1035 patients from 4 centres. Patients underwent elective colorectal resection and were cared for within the context of an ERAS pathway.**

| | All (n=1035) | Colonic (n=724) | Rectal (n=311) | P† |
|---|---|---|---|---|
| M:F | 498:537 | 340:384 | 1:1 | 0.257‡ |
| Age (years)* | 59 (69,78) | 71(59,79) | 65 (57,75) | <0.001§ |
| ASA | | | | |
| 1 | 177 (17.1) | 107(14.8) | 70 (22.5) | |
| 2 | 645 (62.3) | 464(64.1) | 181 (58.2) | |
| 3 | 203 (19.6) | 144(19.9) | 59 (19.0) | |
| 4 | 10 (1.0) | 9(1.2) | 1 (0.3) | <0.001¶ |
| Malignant disease | 710 (69.4) | 501(70.1) | 209 (67.9) | 0.481‡ |
| Neoadjuvant therapy | 15 (1.4) | 5(0.7) | 10 (3.2) | 0.004‡ |
| Time to mobilise (days)* | 3 (2,5) | 3 (2,5) | 3 (2,5) | 0.191§ |
| Total length of stay (days)* | 6 (4,8) | 6 (4,8) | 7 (5,10) | <0.001§ |
| Readmissions | 86 (8.6) | 57 (8.2) | 29 (9.6) | 0.444‡ |
| Anastomotic leaks | 53 (5.1) | 37 (5.1) | 16 (5.1) | 0.982‡ |
| Reoperations | 77 (8) | 56 (8) | 21 (6.9) | 0.563‡ |
| Morbidity (Complications)(30d) | 294 (28.4) | 185 (25.6) | 109 (35.0) | <0.001‡ |
| Mortality (30d) | 17 (1.6) | 14 (1.9) | 3 (0.96) | 0.423‡ |
| Expected morbidity | 430 (41.5) | 259 (35.7) | 171 (55.0) | <0.001‡ |
| Expected mortality | 25 (2.4) | 14 (1.8) | 11.0 (3.3) | 0.156‡ |
| O:E morbidity | 0.69 | 0.71 | 0.64 | |
| O:E mortality | 0.69 | 1.00 | 0.27 | |

Values in parentheses are percentages unless indicated otherwise; *values are median (interquartile range). ASA, American Society of Anesthesioloists; O:E, observed to expected. † colonic *versus* rectal; ‡ chi squared test; § Mann-Whitney U test; ¶ Fisher's exact test.

The complications are summarised in Table 2.2. The most frequent complications were infective, including wound and urinary tract infections. Patients most commonly developed only a single complication. A higher proportion of patients developed one or more complications after receiving mechanical bowel preparation (184 (30·9 %) of 596 versus 106 (24·9 %) of 425 patients having no mechanical bowel preparation; P = 0·041). There were no differences in anastomotic leak rates or 30-day mortality between those who did or did not receive mechanical bowel preparation.

**Table 2.2 Postoperative complications in 1035 patients from 4 centres who underwent elective colorectal resection and were cared for within the context of an ERAS pathway.**

| Type of Complication | | Number of patients |
|---|---|---|
| Cardiopulmonary | Respiratory failure | 23 (2.2) |
| | Pulmonary oedema | 4 (0.4) |
| | Pulmonary embolism | 6 (0.8) |
| | Cardiac failure | 22 (2.1) |
| | Acute MI | 3 (0.3) |
| | Stroke | 2 (0.2) |
| | DVT | 1 (0.1) |
| | Acute Renal Failure | 6 (0.6) |
| Surgical | Wound Dehiscence | 28 (2.7) |
| | Postoperative Bleeding | 29 (2.8) |
| | Anastomotic leak | 53 (5.1) |
| Infective | Wound infection | 128 (12.4) |
| | Pneumonia | 24 (2.3) |
| | Chest infection | 15 (1.4) |
| | Sepsis | 18 (1.7) |
| | UTI | 67 (6.5) |

Values in parentheses are percentages. A total of 741 patients had no complication; 213, 45, 23, eight and five patients had one, two, three, four and five complications respectively.

The results of univariate analysis of the relationship between outcomes and potential outcome predictors are shown in Tables 2.3 - 2.5. BMI category was not related to any of the outcome variables. Age had an influence on time to achieve mobilisation ($P < 0{\cdot}001$) and total hospital stay ($P < 0{\cdot}001$). There was a significant relationship between ASA grade and mobilisation ($P < 0{\cdot}001$), total hospital stay ($P < 0{\cdot}001$) and postoperative morbidity rate ($P = 0{\cdot}003$). Sex influenced postoperative morbidity rate ($P = 0{\cdot}011$). Operation type affected total hospital stay ($P < 0{\cdot}001$) and postoperative morbidity rate ($P = 0{\cdot}002$). The presence of malignancy did not relate to any of the outcomes.

In multivariate analysis independent predictors of delayed mobilisation were age 80 years or more ($P = 0{\cdot}025$) and ASA grade 3 – 4 ($P < 0{\cdot}001$). Prolonged total length of hospital stay was predicted by age 80 years or more ($P = 0{\cdot}002$), ASA grade 3-4 ($P < 0{\cdot}001$), male sex ($P = 0{\cdot}037$) and rectal surgery ($P < 0{\cdot}001$). Postoperative morbidity was predicted by ASA grade 3–4 ($P = 0{\cdot}004$), male sex ($P = 0{\cdot}023$) and rectal surgery ($P = 0{\cdot}002$). Mortality was not related to any of the factors.

**Table 2.3 Univariate analysis of postoperative outcomes according to age, gender, comorbidity, type of surgery and presence of malignancy for 1035 patients from 4 centres who underwent elective colorectal resection and were cared for within the context of an ERAS pathway.**

| | No of Patients | Time to mobilisation (days)* | Total hospital stay (days)* | 30-day morbidity† | 30-day mortality† |
|---|---|---|---|---|---|
| **Body Mass Index (kg/m$^2$)** | | | | | |
| < 20 | 82 | 3 (2,4) | 6 (4,8) | 27 (33) | 1 (1) |
| ≥ 20 | 953 | 3 (2,5) | 6 (4,8) | 267 (28.0) | 16 (1.7) |
| P | | 0.791‡ | 0.820‡ | 0.344§ | 1.000¶ |
| **Age (years)** | | | | | |
| < 80 | 839 | 3 (2,5) | 6 (4,8) | 229 (27.3) | 11 (1.3) |
| ≥ 80 | 194 | 4 (2,6) | 7 (5,11) | 64 (33.0) | 6 (3.1) |
| P | | <0.001‡ | <0.001‡ | 0.113§ | 0.109¶ |
| **ASA grade** | | | | | |
| 1-2 | 822 | 3 (2,5) | 6 (4,8) | 216 (26.3) | 11 (1.3) |
| 3-4 | 213 | 4 (3,6) | 7 (5,12.5) | 78 (36.6) | 6 (2.8) |
| P | | <0.001‡ | <0.001‡ | 0.003§ | 0.133¶ |
| **Sex** | | | | | |
| M | 498 | 3 (2,5) | 6 (4,9) | 160 (25.6) | 11 (2.2) |
| F | 537 | 3 (2,5) | 6 (4,8) | 109 (35.0) | 6 (1.1) |
| P | | 0.986‡ | 0.123‡ | 0.002§ | 0.168¶ |
| **Type of surgery** | | | | | |
| Colonic | 724 | 3 (2,5) | 6 (4,8) | 185 (25.6) | 14 (1.9) |
| Rectal | 311 | 3 (2,5) | 7 (5,10) | 109 (35.0) | 3 (1.0) |
| P | | 0.191‡ | <0.001‡ | 0.002§ | 0.255§ |
| **Types of lesion** | | | | | |
| Malignant | 313 | 3 (2,4) | 6 4,8) | 88 (28.1) | 2 (0.6) |
| Benign | 710 | 3 (2,5) | 6 (4,9) | 203 (28.6) | 13 (1.8) |
| P | | 0.067‡ | 0.161‡ | 0.876§ | 0.254¶ |

*Values are median (interquartile range); †values in parentheses are percentages. ASA, American society of Anesthesiologists. ‡Mann–Whitney U test; §Chi squared test; ¶Fisher's exact test.

**Table 2.4 Multivariate analysis of postoperative recovery outcomes according to BMI group, age group, ASA group, gender, operation type, and malignancy status for 1035 patients from 4 centres who underwent elective colorectal resection and were cared for within the context of an ERAS pathway.**

| | Outcomes | |
|---|---|---|
| Components | **Time to mobilisation** | **Total LOS** |
| BMI Group (<20 kg/m$^2$) | - | - |
| Age Group (≥80 yrs) | 1.18 (1.04-1.34) p=0.012 | 1.16 (1.05-1.28) p=0.002 |
| ASA Group (Grade 3/4) | 1.34 (1.19-1.6) p<0.001 | 1.3 (1.19-1.43) p<0.001 |
| Gender (F) | - | 0.93 (0.86-1) p=0.037 |
| Operation type (Rectal) | - | 1.2 (1.11-1.29) p<0.001 |
| Malignancy | - | - |

Values are: Parameter estimates (95% CI) significance; Values that were not significant in univariate analysis were not included

**Table 2.5 Multivariate analysis of postoperative 30 day morbidity and mortality according to BMI group, age group, ASA group, gender, operation type, and malignancy status for 1035 patients from 4 centres who underwent elective colorectal resection and were cared for within the context of an ERAS pathway.**

| | Outcomes | |
|---|---|---|
| Components | **Morbidity** | **30-day mortality** |
| BMI Group ($<20$ kg/m$^2$) | - | - |
| Age Group ($\geq 80$ yrs) | 1.31 (0.91-1.87) p=0.143 | p=0.186 (NS) |
| ASA Group (Grade 3/4) | 1.61 (1.17-2.22) p=0.004 | p=0.285 (NS) |
| Gender (F) | 0.73 (0.55-0.96) p=0.023 | - |
| Operation type (Rectal) | 1.58 (1.18-2.11) p=0.002 | - |
| malignancy | - | - |

Values are: Odds Ratio (95% CI) significance; Values that were not significant in univariate analysis were not included

## 2.4 Discussion

Within the study presented in this chapter, the overall morbidity rate was 28.4 % and mortality rate was 1.6 %. Morbidity was significantly lower than that predicted by the P-POSSUM system whereas mortality rate was similar to the predicted value. Morbidity and mortality in this cohort were lower than those published for the same units prior to the introduction of an ERAS protocol (morbidity 35 %, mortality 2 %) (Nygren et al, 2005) and for other European units (morbidity 35 - 38.3 %, mortality up to 3.4 %) following traditional care pathways (Braga et al, 2002;Alves et al, 2005). The findings presented in this chapter attest to the safety and potential benefits of the ERAS approach to perioperative care. Median length of hospital stay was 6 days, which is below that published for similar series using traditional care in combination with either open (Nygren et al, 2005) or laparoscopic techniques (Guillou et al, 2005;Veldkamp et al, 2005). The readmission rate of 8.6 % was higher than that associated with traditional perioperative care (Nygren et al, 2005), but was considerably lower than the rate of 20 - 25 % reported for the seminal fast-track programme in Denmark (Basse et al, 2000).

There was good compliance with the preoperative and intraoperative elements of the protocol, however adherence to the protocol fell in the postoperative phase, which is in keeping with previous publications (Maessen et al, 2007). Postoperative variables are both markers of protocol compliance and markers of recovery. Patients achieving the postoperative goals of the protocol are likely to be those making good progress and potentially an accelerated postoperative recovery.

Against the background of such favourable clinical outcomes obtained with the ERAS protocol, the present study demonstrates that neither BMI below 20 kg / $m^2$ nor age 80 years or more were independent predictors of postoperative 30-day morbidity or mortality. The results presented in this chapter suggest that within the context of an enhanced recovery programme the surgeon does not need to individualise postoperative morbidity or mortality risk assessment for elderly or undernourished patients. In contrast, comorbidity is a consistent independent determinant for a range of outcomes.

The mortality rate for those aged 80 years or above was 3.1 %. The outcome from elective colorectal surgery in such elderly patients is variable with reported rates from single institutions as low as 1.1 % (Ong et al, 2008) and from national studies as high as 11.3 % (Heriot et al, 2006). When colorectal patients have been managed using traditional perioperative care, age has been demonstrated repeatedly to be a significant independent predictor of increased mortality after colorectal surgery, even when elderly patients have been selected as 'fit for surgery' (Alley, 2000;Tekkis et al, 2003). Advanced age has also been related to increased postoperative morbidity (Polanczyk et al, 2001) and postoperative pulmonary and renal complications in the elderly have been shown to be independent predictors of decreased long-term survival (Manku et al, 2003). However, if older patients make it through the immediate postoperative period, 5-year survival in those aged 80 years or more is similar to that of the younger group (Smith et al, 2002). This has led to suggestions that an effort to improve perioperative care delivery to elderly surgical patients must include measures to minimise in-hospital postoperative complications, particularly these involving the pulmonary and renal systems (Manku et al, 2003).

The results of the study presented in this chapter suggest that when patients are managed according to an enhanced recovery programme age is no longer an independent risk factor for mortality. This is in keeping with recent meta-analysis (Wind et al, 2006) and suggests that the principles of relatively stress-free surgery and minimisation of organ dysfunction translate into reduced morbidity and the apparent attenuation of the increased surgery risk in the elderly.

Elderly patients are a heterogeneous group and the use of age to predict surgical outcome may be confounded by differences in cancer stage (Alley, 2000), tumour site and most significantly level of comorbidity. However, age is not always associated with increased comorbidity and excellent outcomes for the elderly undergoing major surgery have been documented (Ong et al, 2008). In the series presented in this chapter, age was not significantly related to outcomes other than time to achieve targeted mobilisation and total length of hospital stay on multivariate analysis. The increase in total length of hospital stay itself might be attributed to delayed discharge related to difficulties in arranging social care post discharge (Maessen et al, 2007;Maessen et al, 2008).

In the UK, current guidelines suggest that all patients admitted for major abdominal surgery should undergo nutritional screening (National Institute for Health and Clinical Excellence, 2006). The basis for this recommendation lies with the observation that malnourished patients are at increased risk of postoperative morbidity and mortality and that nutritional support might attenuate such risk. However, routine preoperative nutritional screening has been difficult to achieve and one UK study highlighted that it only took place in 33 % of cases (Murphy et al,

2006). This chapter demonstrates that when patients are managed with an enhanced recovery protocol, a low BMI is not an independent risk factor for adverse outcome and therefore nutritional screening may not be required. The metabolic and nutritional elements of the ERAS protocol designed to minimise catabolism (Soop et al, 2004) may be the basis for such an effect. There are clear limitations to the use of BMI to screen nutritional status. Some patients weigh less than is usual for their height but are otherwise fit and healthy and (in the case of athletes often healthier) and a normal BMI does not exclude the presence of malnutrition. Despite these limitations, BMI is regarded generally as a robust 'field' method especially within a population the size of the present study. BMI is used as part of the nutritional assessment guidelines of The European Society for Clinical Nutrition and Metabolism (ESPEN) (Weimann et al, 2006) and in the Malnutrition Universal Screening Tool (MUST) published by The British Society for Parenteral and Enteral Nutrition (BAPEN, 2003).

Comorbidity is a significant factor in predicting the postoperative outcomes achieved in open surgery (with traditional perioperative care) as evidenced by its use in the POSSUM scoring system (Prytherch et al, 1998), the ASA risk stratification system and most recently in the simplified risk stratification system (Bowles et al, 2008). The present chapter confirms such findings for open surgery combined with enhanced recovery. It has been suggested that ERAS programmes might benefit those with significant cardiorespiratory or renal comorbidity (Kehlet et al, 2002) and this benefit might be most evident in vulnerable sub-groups such as the elderly. The present study demonstrates lower rates of morbidity with use of an ERAS protocol even though 20.6 % of patients had significant comorbidity (ASA 3 or more). Thus, although

comorbidity is still a highly relevant predictor of outcome, it may be modulated beneficially by the ERAS approach.

Rectal surgery and male sex were identified as independent predictors of total length of hospital stay and postoperative morbidity. These associations could be explained by the known increased risk in rectal surgery itself and the greater difficulties of dissection in the male pelvis (Salerno et al, 2006). The present data set was initiated at a time when there was uncertainty about the value of mechanical bowel preparation. Patients who received mechanical bowel preparation had a significantly greater complication rate than those who did not, consistent with the current literature (Slim et al, 2004). The ERAS protocol now recommends the use of mechanical bowel preparation only in specific circumstances (such as low anterior resection with a covering ileostomy on table colonoscopy or small, difficult to palpate tumours).

Within this chapter it is demonstrated that the ERAS protocol represents an overall strategy to condition all patients and to improve all aspects of perioperative care and outcomes rather than the provision of specialised care for a difficult-to-define group of patients. The challenge remains how to optimise further the ERAS protocol. This chapter suggests that a focus on improvement of organ function may be one route forwards. Preoperative metabolic conditioning is explored later in this thesis.

## *Chapter 3. The hepatic resection model: Results from a Phase II study*

### 3.1 Background

The preceding chapter presented the postoperative outcomes achieved within an ERAS programme of care for patients undergoing colorectal surgery and demonstrated that the benefits achieved were also applicable to elderly and undernourished patients. ERAS care protocols have also been applied successfully to open aortic aneurysm repair and oesophageal surgery (Podore et al, 1999;Cerfolio et al, 2004). This chapter examines the application of an Enhanced Recovery After Surgery programme of care for patients undergoing liver resection.

Within traditional perioperative care following liver surgery, median hospital stay ranges from 8 to 14 days (Pessaux et al, 2007). The incidence of postoperative morbidity is also relatively predictable, with haemorrhagic complications occurring predominantly during surgery or in the early postoperative phase, and biliary complications, intra-abdominal abscess or liver failure in the later postoperative phase (Belghiti et al, 2000;Burt et al, 2002). As postoperative outcomes following liver resection are relatively predictable it is ideally suited for the application of an ERAS protocol. The predictable outcomes in this type of surgery also make it a suitable model in which to base randomised controlled trials through which the individual elements of the ERAS programme can be assessed.

This chapter evaluates the feasibility, safety and effectiveness of an ERAS protocol for patients undergoing curative hepatic resection in two European liver units. In this

consecutive case series/control study the postoperative outcomes achieved within the ERAS programme were compared with those achieved within traditional care in the same two units.

## 3.2 Patients and methods

This study was conducted in two surgical units that perform high-volume liver surgery. It was a prospective case series comparing outcomes with those in a historical control group in the same two units.

The ERAS patient group comprised of a consecutive series of 61 patients admitted to either the liver unit in Maastricht University Medical Center, The Netherlands, between 15 February 2005 and 31 August 2006, or the liver unit of the Royal Infirmary in Edinburgh, UK, where patient recruitment started on 1 February 2006. The control group consisted of a consecutive series of 100 patients who underwent liver resection in one of the two units between 1 July 2003 and 31 December 2004 (50 consecutive patients from each unit), when a traditional care pathway was employed. Patient and outcome data were derived from a prospectively collected database of all liver resections performed since 1 January 2000 in both units. In both groups, patients undergoing elective liver resection for primary or secondary tumours were considered eligible for the study if they had normal underlying liver function. Patients were excluded if they required biliary reconstruction or had emergency surgery. In both units, the same group of liver surgeons performed the liver resections in the ERAS group as well as in the control group. In Maastricht more fellows with hepatopancreatobiliary training operated in the ERAS group. Bilateral subcostal transverse abdominal incisions were used. The transection plane was determined by intraoperative ultrasonography. To avoid excessive blood loss central venous pressure was reduced to below 5 mmHg during transection using the Cavitron Ultrasonic Surgical Aspirator (CUSA®; Valleylab, Boulder, Colorado, USA) and argon beam coagulation. The portal pedicles supplying and veins draining the sectors to be

resected were divided and ligated with a running polypropylene suture. After removal of the liver specimen, the raw surface of the liver remnant was subjected to argon beam coagulation and sealed with TachoSil® (Nycomed, Zurich, Switzerland). In accordance with the protocol, no abdominal drains were placed in the ERAS group and the abdomen was closed with a standard running suture.

Before the introduction of the ERAS programme neither of the institutions had a written, agreed perioperative care pathway. There were no specific measures to avoid prolonged preoperative and postoperative fasting, nasogastric decompression, excessive use of intravenous fluids and systemic opioids, prophylactic abdominal drains and postoperative immobilisation. This conventional postoperative care programme emphasized prolonged rest for both the patient and the gastrointestinal tract.

The multimodal ERAS protocol, originally designed for elective colonic surgery, was modified to cover all aspects of elective liver resection (Fearon et al, 2005). Details of the ERAS liver protocol are given in Table 3.1.

**Table 3.1 Care plan for patients undergoing liver resection within the Enhanced Recovery After Surgery programme of care**

| Time period | Protocol element |
|---|---|
| **Day before surgery** | Normal oral nutrition until midnight<br>No preanaesthetic medication |
| **Day of surgery** | Carbohydrate drink 2 hours before surgery<br>Mid-thoracic epidural analgesia (local anaesthetic and low-dose opioid)<br>Short acting IV anaesthetic agent<br>No nasogastric drainage (if used then removed immediately after surgery)<br>Warm IV fluids<br>Intraoperative body warming device<br>Avoidance if excessive IV fluids<br>No routine drainage of the peritoneal cavity<br>Patient sent to recovery ward/HDU<br>Restart oral intake of water/nutrition ad libatum |
| **Postoperative day 1** | Patient mobilises<br>Discontinuation of IV fluids if patient drinks at least 1.5 litres of fluid<br>Normal diet<br>Continuation of epidural analgesia (local anaesthetic and low-dose opioid)<br>1g paracetamol QDS<br>1 g magnesium hydroxide BD |
| **Postoperative day 2** | Continuation of epidural analgesia (local anaesthetic and low-dose opioid)<br>Continue mobilisation<br>1g paracetamol QDS<br>1 g magnesium hydroxide BD<br>Normal diet |
| **Postoperative day 3** | Stop epidural, Removal of urinary catheter<br>Commence NSAIDs<br>Continue mobilisation and normal diet<br>Review discharge criteria |
| **Postoperative day 4** | Review discharge criteria and discharge when achieved |

The above table is based on Table 2.1 presented earlier in the present thesis

In both groups, data were obtained prospectively during the hospital stay and for 30 days after surgery. Data recorded for each patient included morbidity, defined as complications related to the liver surgery, mortality, readmissions, postoperative hospital stay, use of preoperative chemotherapy, duration of surgical procedure, blood loss, anaesthetic agents used and extent of liver resection. Extent of liver resection was defined according to Brisbane 2000 terminology (International Hepato-Pacreato-Biiary Association, 2000). Following implementation of the ERAS protocol data on epidural use, removal of the nasogastric tube if used, and time to resumption of oral intake and mobilisation were also recorded.

The primary endpoint of this study was total length of hospital stay, which was defined as the number of nights spent in hospital, including nights after readmission within 30 days of surgery. To facilitate objective assessment of clinical outcome predefined discharge criteria were used in the ERAS group (Table 3.2). Patients received preadmission counselling and were informed about the protocol prior to admission to hospital. Elements such as the importance of early mobilisation and early oral intake were explained. Patients were discharged only if they met the discharge criteria. Patients were given a mobile telephone number of the surgical team or myself to allow direct communication and safe deployment of the protocol. Patients in the control group were discharged without formal discharge criteria.

**Table 3.2 Objective criteria to indicate eligibility for hospital discharge for patients managed within an ERAS programme of perioperative care.**

| |
|---|
| Pain control with only oral analgesia |
| Tolerance of solid food |
| No requirement for IV fluids |
| Independently mobile or back at preoperative level |
| Blood tests returning towards normal ranges |
| All of the above and willing to go home |

The following secondary endpoints were evaluated: resumption of oral intake, defined as oral intake of water or normal food without discontinuation for at least 24h, readmissions to hospital, total morbidity, death and length of primary hospital stay (defined as the number of nights spent in hospital after surgery excluding readmissions). Complications were registered during the primary admission or at subsequent outpatient clinic visits up to 30 days following surgery.

**Statistical analysis**

Continuous data are expressed as median (range). Hospital stay, time to resumption of oral intake and postoperative duration of epidural analgesia were analysed using the Mann–Whitney U test. Readmission, complication and mortality rates were analysed using chi-squared test or Fisher's exact test. $P < 0{\cdot}050$ was considered to be statistically significant. Data were analysed using SPSS® version 13.0 for Windows® (SPSS, Chicago, Illinois, USA).

## 3.3 Results

Patient characteristics were similar in the ERAS and control groups (Table 3.3). Extent of liver resection is shown in Table 3.4. A higher proportion of patients in the ERAS group underwent repeat resections (11 % versus 5 % in control group; $p = 0{\cdot}214$) and resections after intensive chemotherapy (62 versus 33 %; $p < 0{\cdot}001$).

**Table 3.3 Demographics and underlying pathology of 61 patients managed within an ERAS care programme compared with 100 patients managed within traditional care.**

| | ERAS (n=61) | Control (n=100) |
|---|---|---|
| Age (years)* | 62 (24-82) | 60 (20-81) |
| Sex ratio (M:F) | 35:26 | 51:49 |
| ASA grade | | |
| 1 | 11 (18) | 14 (14.0) |
| 2 | 42 (69) | 64 (64.0) |
| 3 | 8 (13) | 22 (22.0) |
| Liver pathology | | |
| Colorectal metastases | 51 (84) | 72 (72) |
| Other metastases | 2 (3) | 4 (4) |
| Hepatocellular carcinoma or cholangiocarcinoma | 4 (7) | 9 (9) |
| Benign lesion | 4 (7) | 14 (14) |
| T4 invasive tumours in liver | 0 (0) | 1 (1) |

Values in parentheses are percentages unless indicated otherwise; *values are median (range). ERAS, Enhanced Recovery After Surgery; ASA, American Society of Anesthesiologists.

**Table 3.4 Extent of liver resection: 61 patients managed within an ERAS care programme and 100 patients managed within traditional care**

| | ERAS (n = 61) | Control (n = 100) |
|---|---|---|
| Hemihepatectomy | 20 (33) | 38 (38) |
| Hemihepatectomy + ≥ 1 metastasectomies | 6 (10) | 16 (16) |
| Extended hemihepatectomy | 7 (11) | 3 (3) |
| Multiple segmentectomy (≥ 2 segments) | 17 (28) | 18 (18) |
| Central resection/ trisectionectomy | 1 (2) | 4 (4) |
| Matastasectomy or monosegmentectomy | 10 (16) | 21 (21) |
| Repeat hepatectomy | 7 (11) | 5 (5) |

Values in parentheses are percentages.

The median (range) duration of surgery was 220 (60 – 420) minutes in the ERAS group and 270 (106 – 510) minutes in the control group ($P < 0{\cdot}001$) and blood loss during surgery was 750 (0 – 5000) and 800 (0 – 6000) ml respectively ($P = 0{\cdot}758$). Abdominal drains were used significantly less often in the ERAS group (2 versus 66 %; $P < 0{\cdot}001$).

In Edinburgh, the use of a nasogastric decompression tube in patients having partial liver resection had already been discontinued before 1 July 2003. In Maastricht, nasogastric decompression tubes were still used in most control patients. A nasogastric tube was inserted at induction in 37 of 47 patients in the ERAS group (Maastricht), significantly less frequently than in the control group (96%) ($P = 0{\cdot}013$). In the ERAS group, the nasogastric tube was removed at the end of surgery or in the recovery ward within 4 h of surgery.

Oral intake was resumed within 4 h of surgery in 56 patients (92 %) in the ERAS group. Two patients required reinsertion of a nasogastric tube. The median (range) time to successful resumption of normal diet was 1 (0 – 3) day in the ERAS group, compared with 3 (0 – 14) days in control group ($P < 0{\cdot}001$). Three patients in the ERAS group (5 %) became constipated after postoperative day 3, despite initial tolerance of normal food, but this resolved within 5 days. In the ERAS group, 58 patients (95 %) followed the anaesthetic protocol of mid-thoracic epidural analgesia commencing before surgery (0·1 per cent bupivacaine + 2 μg/ml fentanyl) with maintenance isoflurane or sevoflurane inhalation anaesthesia, or intravenous propofol, as described previously (Fearon et al, 2005). After surgery continuous epidural analgesia comprising 0·1% bupivacaine and 2 μg/ml fentanyl was administered for at

least 3 days at a rate of 4 – 10 ml/h and combined with oral, non-opioid analgesia. This was different from the control group. Although 89 patients (89 %) received epidural analgesia combined with isoflurane or sevoflurane inhalation anaesthesia. In the postoperative period epidural analgesia consisting of 0·1 per cent bupivacaine and 2 μg/ml fentanyl was administered without a specific time schedule at a daily fixed dose of 4 – 10 ml/h, combined with intramuscular opioids and oral analgesia. Postoperative epidural analgesia was continued for a median (range) of 3 (1–5) days in the ERAS group and 2 (0 – 6) days in the control group ($P < 0·001$). Epidural analgesia was discontinued earlier in the control group, and intramuscular or intravenous opioids were used more frequently.

Outcome data are summarized in Table 3.5. There were no deaths in the ERAS group but one patient died within 30 days in the control group. A further control patient died after 62 days. Overall morbidity rates (percentage of patients with at least one complication) were 41 % and 31 % in the ERAS and control groups respectively ($P = 0·197$) (Table 3.6). All complications in the ERAS group were managed by non-surgical means. Readmission rates in ERAS and control groups were similar (13 % versus 10 % respectively; $P = 0·610$). Fifty-two (85 %) of 61 patients in the ERAS group were completely mobile on the third day after operation and 29 (48 %) were discharged from hospital within 5 days. Median (range) total postoperative hospital stay, including readmissions, was 6·0 (3 – 82) days in the ERAS group and 8·0 (4 – 68) days in the control group ($P < 0·001$) (Fig. 3.1).

**Table 3.5 Postoperative outcome data: 61 patients undergoing hepatic resection managed within an ERAS programme of care and 100 patients undergoing hepatic resection within traditional perioperative care**

| | ERAS | Control | P |
|---|---|---|---|
| **Maastricht only** | (n=47) | (n=50) | |
| NGT | 37 (79) | 48 (96) | 0.013‡ |
| Removal of nasogastric tube on day of surgery | 34 of 37 (92) | 0 of 48 (0) | < 0.001 |
| **Maastricht and Edinburgh** | (n=61) | (n=100) | |
| Epidural analgesia | 58 (95) | 89 (89) | 0.184‡ |
| Abdominal drain | 1 (2) | 66 (66) | < 0.001‡ |
| Complications | 24 (41) | 31 (31) | 0.197‡ |
| Death | 0 (0) | 2 (2) | 0.526 |
| Readmission | 8 (13) | 10 (10) | 0.543‡ |
| Total Hospital stay (including readmissions) 9days)* | 6 (3-82) | 8 (4-68) | < 0.001 |
| Primary hospital stay (days)* | 6 (3-82) | 8 (4-55) | < 0.001 |

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Nasogastric tubes (NGTs) were used in Maastricht only; they were used in neither group in Edinburgh. ERAS, Enhanced Recovery After Surgery. P values by Fisher's exact test, except ‡ Chi squared test.

**Table 3.6 Postoperative complications: 61 patients undergoing hepatic resection managed within an ERAS programme of care and 100 patients undergoing hepatic resection within traditional perioperative care**

| | **ERAS** (n=61) | **Control** (n=100) | **P*** |
|---|---|---|---|
| No of patients with complications | 25 (41) | 31 (31) | 0.197† |
| Bile leak | 4 (7) | 4 (4) | 0.479 |
| Liver failure | 3 (5) | 1 (1) | 0.153 |
| Sepsis | 0 (0) | 1 (1) | 1.00 |
| Abdominal collections | 5 (8) | 7 (7) | 0.779† |
| Delayed GI function (>7 day) | 3 (5) | 1 (1) | 0.153 |
| Pneumonia | 3 (5) | 2 (2) | 0.368 |
| Pleural effusion | 2 (3) | 2 (2) | 0.634 |
| Pulmonary embolism | 0 (0) | 1 (1) | 0.433 |
| Myocardial infarction | 2 (3) | 3 (3) | 0.921 |
| Wound infection | 9 (15) | 5 (5) | 0.033† |
| Other Minor | 3 (5) | 16 (16) | 0.018† |

Values in parentheses are percentages. ERAS, Enhanced Recovery After Surgery; GI, gastrointestinal. *Fisher's exact test, except †Chi squared test.

**Fig 3.1 Total length of hospital stay, including any period following readmission to hospital: 61 patients undergoing hepatic resection managed within an ERAS programme of care and 100 patients undergoing hepatic resection within traditional perioperative care**

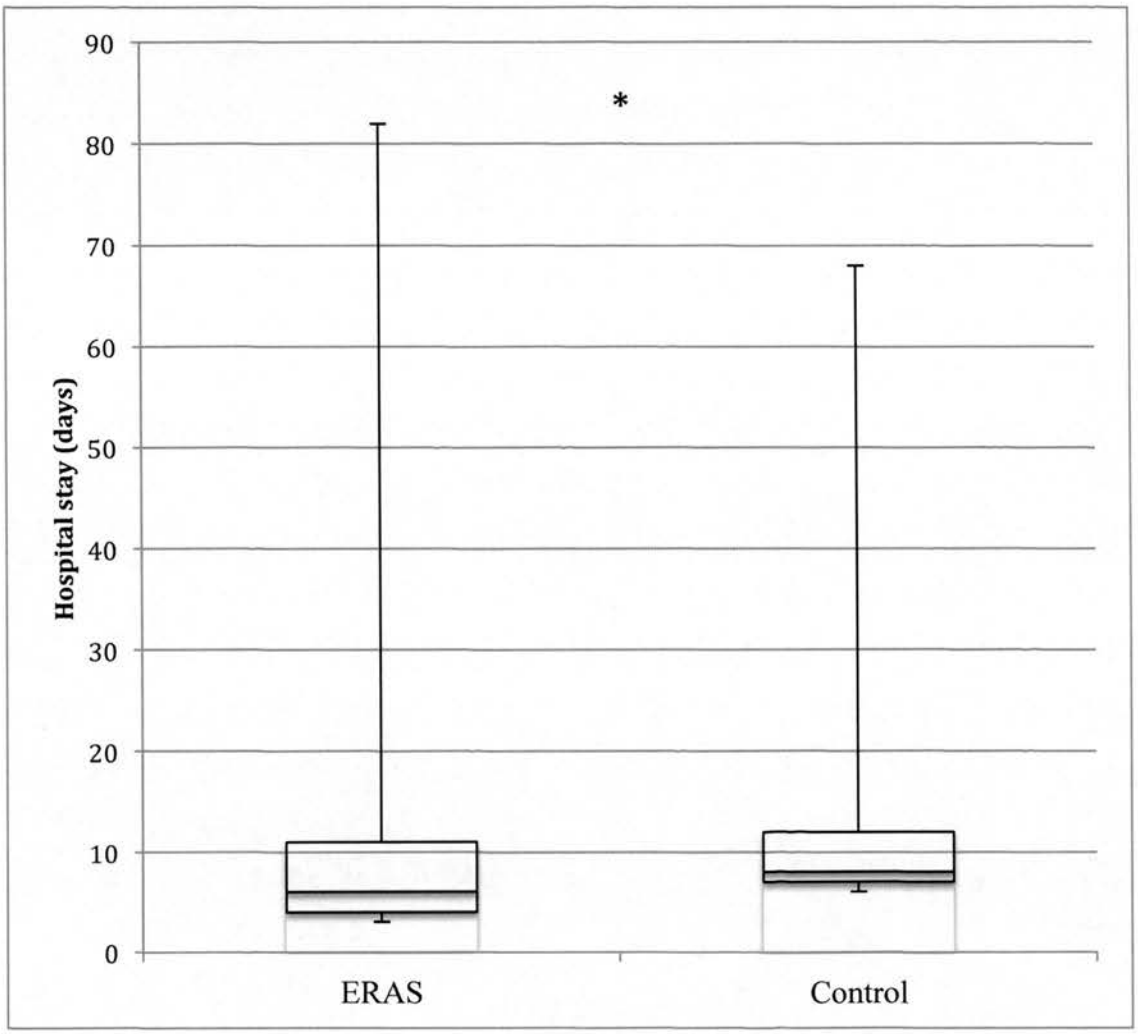



**Fig. 1** Horizontal lines within boxes, boxes and error bars represent median, interquartile range and total range respectively. *P < 0·001 (Mann–Whitney U test)

## 3.4 Discussions

The case / control series presented within this chapter demonstrates that application of an evidence-based multimodal enhanced recovery programme after liver resection can accelerate postoperative recovery and result in a significantly shorter hospital stay. Patients managed within this protocol were able to drink fluids within 4 h of liver resection and return to normal diet on the day following surgery. Most patients were mobile after 3 days and almost half were discharged within 5 days of surgery. Median total hospital stay (including readmissions) was reduced from 8 to 6 days. This is considerably shorter than the 8 – 14 days reported by other European centres (Jarnagin et al, 2002;Dimick et al, 2004;Capussotti et al, 2006). Application of the ERAS protocol did not have any detrimental effect on postoperative morbidity rate.

Based on previous experience of enhanced recovery implementation studies within these units, and attempts to randomise between fast-track and traditional care in a multicentre abdominal surgery trial (Maessen et al, 2007), a randomised clinical trial comparing fast-track and traditional care was considered impractical. ERAS protocols had been implemented over the previous years in both units in view of the growing evidence base for such programmes a traditional perioperative care protocol was felt to represent suboptimal care. Therefore it was felt more appropriate to compare the prospective ERAS group with a historical control group.

The study presented in this chapter demonstrates that adverse outcomes (rate of hospital readmission, postoperative complications and death) following liver resection were similar for both the ERAS and control groups. The complication rate in the

ERAS group was in keeping with recently published rates of 23 - 52 % (Jarnagin et al, 2002;Petrowsky et al, 2006;Schroeder et al, 2006;Benzoni et al, 2007;Figueras et al, 2007). Although the morbidity rate was higher in the ERAS group, the study was not sufficiently powered to determine statistical differences in the incidence of postoperative complications. Moreover, complications directly related to liver surgery, such as bleeding, bile leakage or temporary liver failure, are unlikely to be influenced by postoperative care. Avoidance of abdominal drains in this study might arguably have influenced the complication rate, however, the incidence of bile leak and intra-abdominal collection was similar in the two groups. Prophylactic drains are employed in many centres to detect early complications such as postoperative haemorrhage or bile leakage, however, there is no evidence that abdominal drainage after liver resection aids diagnosis of such an event, reduces their incidence or provides sufficient drainage for these complications if they arise (Fong et al, 1996;Petrowsky et al, 2004). Some studies have suggested that drains may be detrimental to clinical outcome by providing a route for ascending infections and noted higher rates of infected collections when drainage was used (Fong et al, 1996;Burt et al, 2002;Liu et al, 2004). The main disadvantage of drains within an enhanced recovery setting is that they represent a significant impediment to achieving early mobilisation.

Despite the existing evidence base for the ERAS programme it has not been universally accepted (Kehlet et al, 2006). The use of carbohydrate drinks before surgery reduces thirst, hunger and anxiety, and is safe up to 2 h before abdominal surgery (Nygren et al, 1995;Brady et al, 2003). However, a preoperative fasting policy of 'nil by mouth from midnight' is still common in many surgical units.

Nasogastric decompression tubes were still commonly used during surgery in both groups in Maastricht owing to tradition in the anaesthesia department. In the ERAS group they were removed immediately after surgery, which was a major change in clinical routine. Nasogastric decompression is still used commonly following abdominal surgery (Kehlet et al, 2006), despite evidence that it is unnecessary and can result in more pulmonary complications (Cheatham et al, 1995;Nelson et al, 2007). Further support for avoidance of nasogastric tubes specifically in liver surgery has been published recently (Pessaux et al, 2007).

Early postoperative enteral nutrition compared with 'nil by mouth' improves clinical outcome (Lewis et al, 2001;Andersen et al, 2006). Early resumption of normal diet in combination with other elements of the enhanced recovery programme such as a restrictive perioperative intravenous fluid regimen (Lobo et al, 2002) is designed to reduce the occurrence of delayed gastrointestinal function after surgery and to promote overall recovery. In the study presented in this chapter, oral intake of water was tolerated within 4 h after surgery and recommencement of oral diet on the day after surgery in the ERAS group. Delayed return of gastrointestinal function, which was observed in a few patients, was recorded as a postoperative complication.

It is important that surgical patients are treated in an environment that encourages mobilisation in the early postoperative period (Kehlet et al, 2002), and provided with both adequate pain control and support from the nursing staff. Mobilisation on the day of surgery was possible in Edinburgh, but proved difficult in Maastricht as this setup did not exist.

In conclusion, this chapter presents a prospective case series of patients undergoing curative resection of primary or secondary liver tumours with otherwise normal hepatic function within a multimodal enhanced recovery programme. The programme of care was found to be both feasible and effective. Patients were able to drink within 4 h of surgery, eat on the following day and were mobile by the third day after surgery. This early recovery and was accompanied by a reduction in median length of hospital stay from 8 to 6 days. Half of the patients were discharged within 5 days and with increased familiarity with the protocol further reductions in length of stay may be possible. The study demonstrates that ERAS principles developed for the colorectal model can be easily applied to other types of abdominal surgery.

# SECTION D. DEVELOPMENT OF NOVEL POSTOPERATIVE OUTCOMES AND MARKERS OF RECOVERY

Current postoperative outcomes utilised as endpoints in the existing ERAS studies are often both markers of compliance and markers of recovery (Maessen et al, 2007). It has also been demonstrated that variables outwith the control of a perioperative care programme will influence length of hospital stay (Maessen et al, 2008). This section of the thesis explores novel markers of recovery that may provide a more objective measure of postoperative recovery rate. These outcomes may be of use in future ERAS trials.

## *Chapter 4. Development of the $^{13}C$ isotope gastric emptying breath test as a marker of overall recovery*

### 4.1 Background

Within traditional perioperative care transient, postoperative gastrointestinal dysfunction is accepted as an obligatory consequence of major abdominal surgery. In some cases this dysfunction may persist as ileus beyond the early period. It is unclear why the gastrointestinal tract follows this pattern, as postoperative gastrointestinal dysfunction does not appear to provide any protective benefit. The severity of postoperative gastrointestinal dysfunction is usually related to the degree of trauma or handling of the bowel (Kalff et al, 1998). Immobility and administration of systemic opiates in the postoperative period exacerbate this gastrointestinal dysfunction (Holte et al, 2002;Ludwig et al, 2008) and measures such as mid-thoracic epidural (Miedema et al, 2003) and avoidance of excessive intravenous sodium and water (Lobo et al, 2002) facilitate its recovery.

Appropriate assessment of postoperative gastrointestinal function is difficult. Surrogate endpoints such as passage of flatus or stool are used as markers of gut recovery, however, first passage of stool following surgery only addresses excretory bowel function. The stomach recovers some activity within 24 hours and the small intestine demonstrates contractile activity within hours of surgery (Catchpole, 1989;Miedema et al, 2003). First passage of stool is not an early marker of recovery as patients may already be mobile, tolerating diet and ready for discharge (Andersen et al, 2006). Within existing ERAS trials these surrogate measures of gastrointestinal function are used along with endpoints that are themselves protocol elements, therefore achievement of these outcomes overlaps with protocol compliance (Maessen

et al, 2007). Gastric emptying may, therefore, be a more objective measure of recovery in the early postoperative phase.

Early postoperative feeding is associated with both reduced mortality and hospital stay, however, it can result in bloating and vomiting (Andersen et al, 2006). To effectively facilitate early diet a multimodal regimen is required to minimise nausea, vomiting and ileus (Kehlet et al, 2001;Delaney et al, 2006). Although the ERAS package of care has been shown to promote early tolerance of oral diet (Holte et al, 2000;Basse et al, 2002) currently it is unclear which specific elements of the protocol are most significant. Measurement of postoperative gastric emptying may be an effective, reproducible and objective endpoint through which these individual elements could be assessed and may also be a useful predictor of postoperative nausea and vomiting, the ability to start oral diet or anticipated hospital stay (Walldén et al, 2006).

There are a number of methods available to assess gastric emptying, each with its own advantages and disadvantages. Each technique requires a different level of specialist equipment and expertise. Results vary depending on the methodology employed (Bratten et al, 2006). Although scintigraphy is often considered the gold standard assessment of gastric emptying allowing accurate, non-invasive assessment of solid and liquid phase gastric emptying (Lobo et al, 2002), it requires the administration of a radioisotope, use of specialised equipment and is not suitable in many groups of patients. The $^{13}C$ labelled stable isotope breath test (SIBT) would appear to be an attractive alternative as this test is easy to perform, does not involve any radiation exposure and can be used repeatedly in the same subject. This test is

relatively inexpensive and is applicable to field testing because the collected breath samples are stable and can be sent to a central laboratory for analysis (Schoeller, 2005). Although SIBT is an indirect measure of gastric emptying, (measuring the rate at which $^{13}CO_2$ is exhaled in breath, rather than the rate at which $^{13}$C-Na Acetate is emptied from the stomach) this is taken into consideration in the self-correcting model described by Bluck and Coward (Bluck et al, 2006). When this model is applied to the raw data from SIBT the results are directly comparable with direct measurement methods such as scintigraphy

This chapter explores the use of SIBT to assess gastric emptying rate as a marker of postoperative recovery and a potential objective outcome measure for use in future ERAS studies. The data was obtained as part of a larger randomised controlled trial presented in Chapter 8. The feasibility of the technique as a bedside test in the postoperative period was assessed and patient acceptability documented. In addition comparison was made with a) traditional indices of return of gastrointestinal function b) outcome measures of overall recovery

## 4.2 Patients and methods

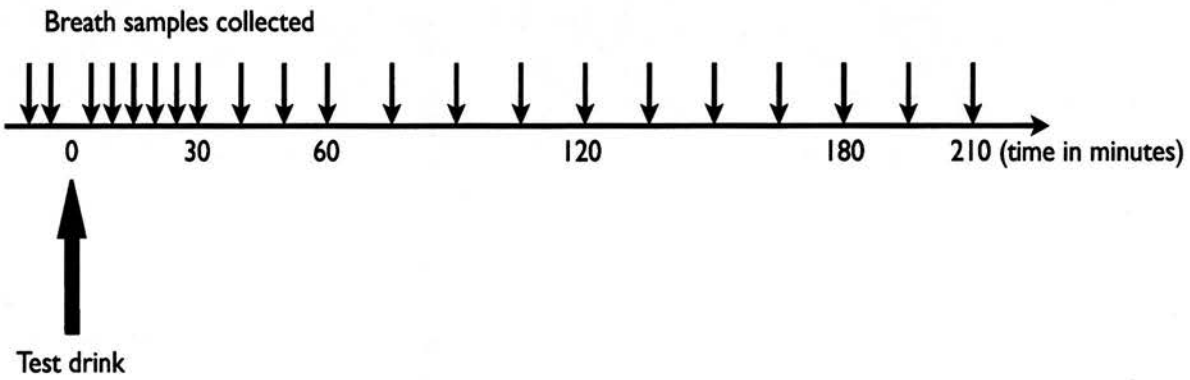
All patients undergoing breath testing were programmed to undergo hepatic resection for benign or malignant conditions at the Liver Unit at Edinburgh Royal Infirmary Edinburgh, UK, between July 2006 and June 2008. All were aged between 18 - 80 years of age, had a BMI of between 18 and 30 $Kg/m^2$ and had no pre-existing limitations to mobility or underlying cirrhotic liver disease. Informed, written consent was obtained from all patients recruited.

Patients followed a standardised perioperative and anaesthetic regimen based on a previously published ERAS protocol (Fearon et al, 2005). On the third postoperative day following an overnight fast, patients underwent assessment of gastric emptying rate of a 200 ml liquid test meal, which contained 36.8 g of carbohydrate, 12 g of protein and 11.6 g of fat (Nutricia Fortisip® nutritional supplement (Appendix A) through a non-invasive stable isotope (sodium $^{13}$C-acetate) breath test (Braden et al, 1995). After an overnight fast two basal breath samples were collected. For each breath test sample the subject was asked to exhale through a drinking straw into a 12 ml screw topped glass Exetainer tube. The patients then ingested 50 ml of the oral sip feed (Fortisip, Nutricia®) containing 75 mg of sodium $^{13}$C-acetate (Cambridge isotopes, USA), the remainder of the 200 ml of drink was ingested promptly as the patient's comfort level allowed.

A further 19 breath samples were taken, in a similar fashion to the first two. These occurred every 5 minutes for the first 30 minutes, every 10 minutes until 60 minutes and then every 15 minutes until 3.5 hours after the initial tracer was ingested (See Fig 4.1). During the test period activity was restricted (Slater et al, 2006) and subjects

remained in a sitting position (Moore et al, 1988). The breath samples in the exetainers tubes were analysed within 5 days. Previous studies have shown that samples remain unchanged for over 60 days post collection (Schoeller, 2005).

Fig 4.1. Diagram of gastric emptying, stable isotope breath testing protocol.



**Analysis of $^{13}CO_2$ enrichment in exhaled breath**

The $^{13}CO_2$ enrichment of breath samples ($^{13}C$:$^{12}C$ ratio) was measured by automated continuous-flow Isotope Ratio Mass Spectrometry (Preston et al, 1988) and the unit $PDRh^{-1}$ or percentage dose recovered per hour calculated as the product of $^{13}C$ enrichment and volume flow rate of $CO_2$ ($VCO_2$) in exhaled breath. $VCO_2$ was estimated from resting $VCO_2$, which was predicted from body surface area and applying a physical activity level of 1.3 (Slater et al, 2006). Cumulative output (cPDR) was then derived by differentiating the $PDR^{-1}$ data.

The raw data for percentage of dose recovered per hour along with the Seigel curve fit (Siegel et al, 1988) was according to the following equation:

$$B(t)+mk\beta(1-\exp(-kt))^{\beta-1}\exp(-kt)$$

An example graph of this data is presented in Fig 4.2. B(t) is the breath test output, m is the area under the curve, k is a rate constant and β a constant which describes the decay. $T_{1/2}$ of breath appearance is calculated according to the equation:

$$T_{1/2}=(-1/k)*Ln(1-1/2^{1/\beta}).$$

The self-correcting model takes the form:

$$G(t)=G(\beta(1-\exp(-kt))^{\beta-1}-(\beta-1)(1-\exp(-kt))^{\beta}.$$

Where G is the gastric output. GE $T_{1/2}$ is derived by interpolation. The self-correcting model assumes that the bicarbonate kinetics can be described using a single body pool and accounts for the delay in appearance of $^{13}CO_2$ in breath (Bluck et al, 2006) (Fig 4.3). The test drink remaining in the stomach (retention) is the inverse of the self-correcting cumulative output line (Fig 4.4).

The data reduction presented in this chapter was facilitated using Microsoft Excel® and a semi-automated spreadsheet template (designed by Prof T Preston) (Bluck et al, 2006). The raw IRMS data is entered into the template spreadsheet where prepared formulae calculate and predict PDRh-1 using estimates of the parameters *m, k & b* from the Seigel fit. The sum of squares of the difference between measured and predicted values is calculated. The SOLVER function is used for non-linear curve fitting by minimising the sum of squares through iteratively adjusting the three parameters of the Seigel fit. As the self-correcting model uses the same three parameters, its output is produced and graphed automatically. GE T1/2 is calculated using the GOAL SEEK function to facilitate estimation of the time when half the area under the curve has appeared (*m*/2).

The 'self corrected' $T_{1/2}$ was used to assess the rate of gastric emptying. Gastric emptying rate was considered delayed when the $T_{1/2}$ was above the 90$^{th}$ percentile.

**Fig 4.2 Example output from breath test data with percentage dose recovered per hour and Seigel curve fit.**

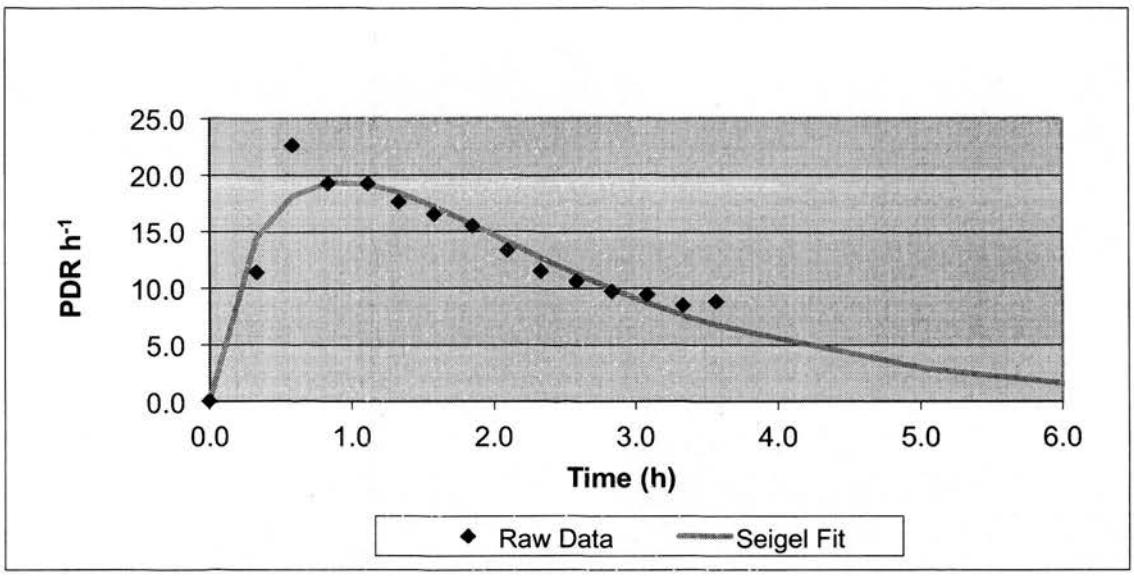


**Fig 4.3 Example output from breath test data with Cumulative dose recovered and Seigel curve fit.**

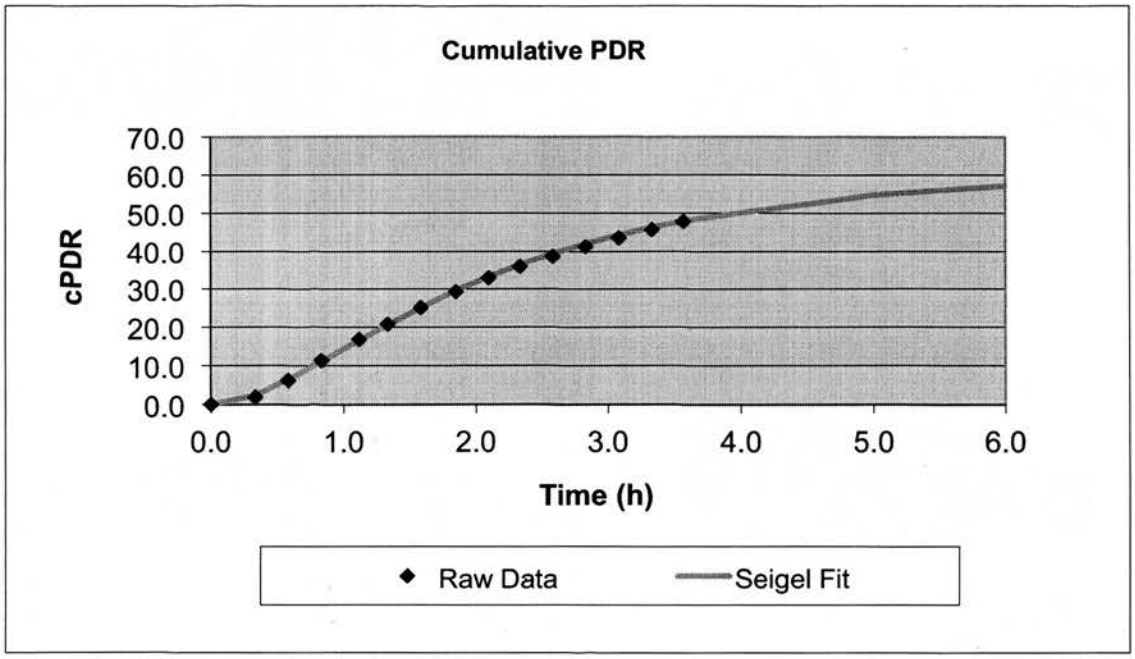
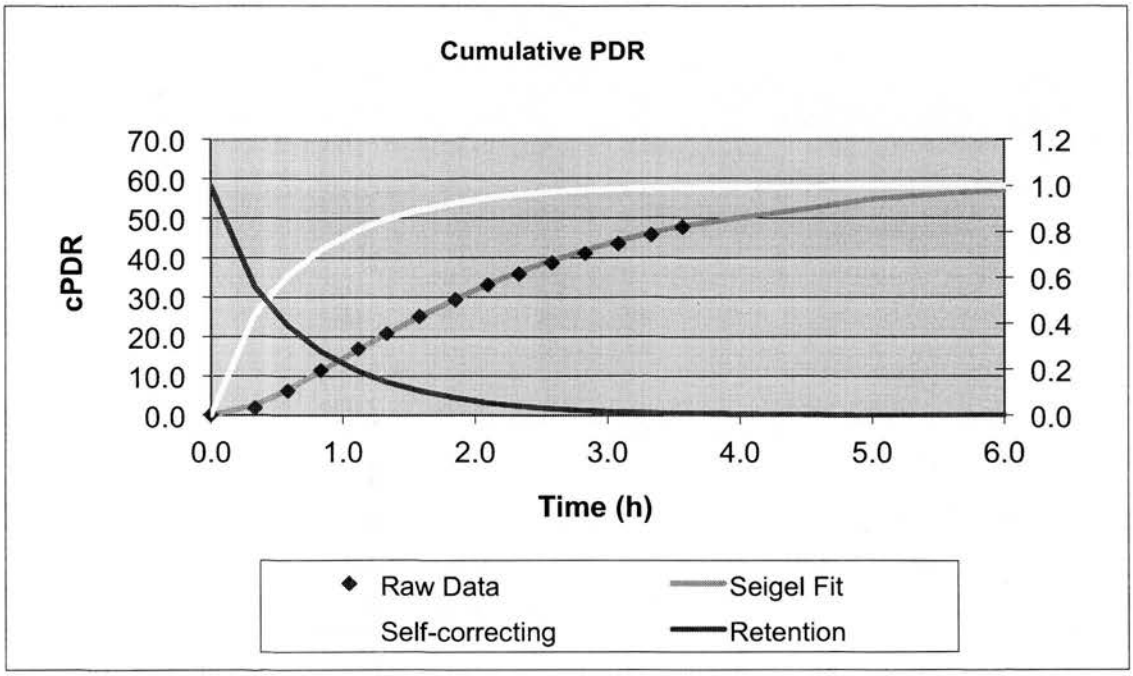


**Fig 4.4 Example output of breath test data and application of self-correcting model and fluid retention line**

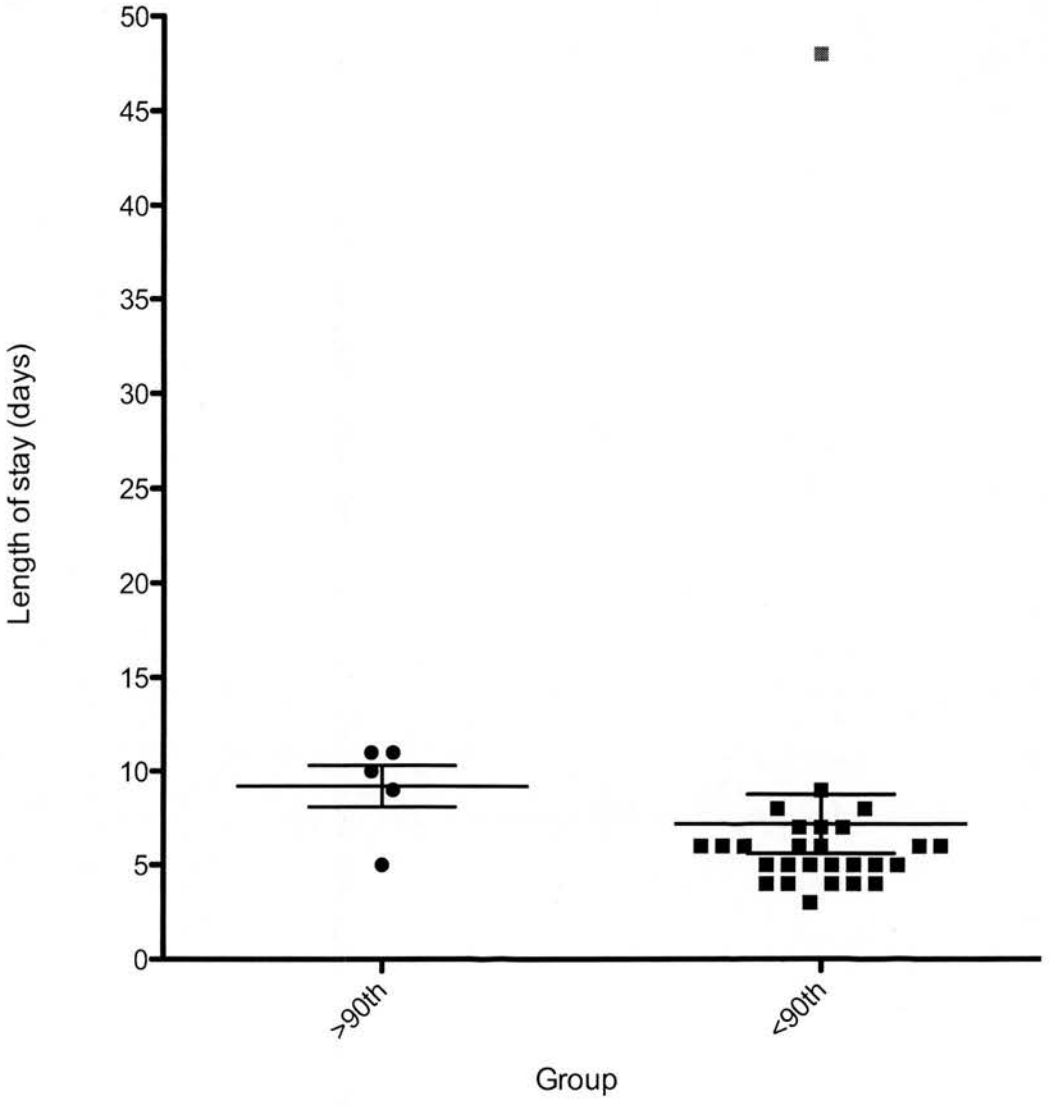


## 4.3 Results

Of fifty-six patients who were eligible to participate in the gastric emptying protocol 32 underwent stable isotope breath testing. All, participating patients tolerated the protocol with only one subject complaining of nausea and vomiting shortly after completing the test. For the group overall the male to female ratio was 19:13, median (IQR) age was 62 (52,68) years and median (IQR) BMI 27 (25,30). All patients were ASA grades I-III, twenty-seven patients (84.4 %) were treated for malignant disease and there were 21 major and 11 minor resections.

Oral fluid intake was resumed on the day of surgery in 94 % of patients. Reintroduction of diet was achieved on day one in 47 % of patients and by day two in 96 % of patients. Time to first passage of stool and length of hospital stay were 5 (5,6) and 5 (5,7.75) [median (IQR)] days respectively. Overall postoperative gastric emptying ($T_{1/2}$) was 0.74 (0.46,1.41) hours [median (IQR)]. A small number of subjects (n=5) had significantly delayed gastric emptying ($T_{(1/2)} > 1.677$ hours ($90^{th}$ percentile). In comparison with the rest of the patients undergoing measurement of gastric emptying rate (n=27), the group with a significantly delayed gastric emptying time also had a significantly prolonged length of hospital stay (10 (7,11) v 6 (5,7) days [median (IQR)]: p=0.019) (see Fig 4.5). There were no significant differences between these two groups for other postoperative outcomes (Table 4.1).

**Fig 4.5 Comparison of group of patients with significantly delayed gastric emptying**




Comparison of individual groups made with Mann-Whitney Test. P=0.019

**Table 4.1 Comparison of outcomes for patients with significantly delayed GE (>90$^{th}$ percentile) and patients with normal GE (<90$^{th}$ percentile) on postoperative day three**

| | > 90$^{th}$ percentile | < 90$^{th}$ percentile | p† |
|---|---|---|---|
| Return to oral diet | 1 (0,3) | 1 (0,1) | 0.608 |
| IV fluids stopped | 1 (1,5.5) | 1 (1,2) | 0.590 |
| Passage of flatus | 3 (1.25,4.75) | 2 (1.5,3) | 0.746 |
| Passage of stool | 5 (4,5.5) | 5 (3,6) | 0.770 |
| Achieve discharge criteria | 5 (4,7) | 4 (3,5) | 0.112 |
| Length of hospital stay | 10 (7,11) | 6 (5,7) | 0.019 |

All values are median (interquartile range), †Mann Whitney.

## 4.4 Discussion

Postoperative gastrointestinal dysfunction is often considered an unavoidable consequence of major abdominal surgery. Patients managed within an ERAS programme of care often have improved postoperative gastrointestinal function and an earlier tolerance of oral diet (Holte et al, 2000;Basse et al, 2002). The ERAS protocol overall has been demonstrated to improve postoperative recovery, however, future ERAS trials would hope to evaluate the contribution of individual elements to this improved recovery. Current markers of postoperative gastrointestinal function (first passage of stool) may not be sensitive enough to differentiate the contribution of these specific protocol elements. Upper gastrointestinal function recovers more quickly than lower gastrointestinal function following major abdominal surgery (Catchpole, 1989), therefore gastric emptying time in the early postoperative period may be a more useful measure of gastrointestinal recovery. Such a measurement may predict the success of early postoperative feeding and may be of use in assessing the efficacy of individual elements of a perioperative care pathway.

This chapter presents SIBT as an acceptable method of investigating gastric emptying rate within days of major abdominal surgery. One patient complained of nausea during the protocol, which correlated with a significantly delayed gastric emptying. There were no other complications or side effects. This is in keeping with other studies that have employed this method of assessment in children, neonates and the critically ill (Chioléro et al, 2003;Braden et al, 2004). Nine patients refused the SIBT but this was due to the test feed employed rather than the breath sampling protocol itself. Oral sip feed (Fortisip, Nutricia®) was selected due to its availability but could

be replaced with other test meals. The test was also impractical for fifteen patients who had not yet been discharged from HDU as expected.

Although much of the available literature refers to gastric emptying of solids in the present protocol it was more feasible to assess gastric emptying of liquids as patients would tolerate fluids earlier. An energy rich liquid test meal (Nutricia Fortisip®) was employed in this protocol. This test meal is readily available, inexpensive, is often used in postoperative patients to supplement inadequate diet, is generally well tolerated by patients and is available in a variety of flavours. A calorie rich liquid empties more slowly than a non-calorie containing liquids (Hellström et al, 2006) potentially facilitating clearer differentiation of gastric emptying rate between subjects.

The protocol presented here uses a Na $^{13}$C-acetate tracer (Braden et al, 1995), which imposes no risk due to ionizing radiation. The Stable Isotope Breath test can be performed while the patient is sitting and even accommodates ambulation. This test is therefore ideally suited for the early postoperative period. With sufficient refinement of the protocol and adequate instruction it may even be possible for patients to collect his or her own breath samples at the appropriate scheduled times. This facilitates testing multiple patients simultaneously. As the analysis of the breath samples can be performed after a delay of up to sixty days the IRMS facility does not have to be nearby (Schoeller, 2005).

Although the $^{13}$C-acetate breath test is an inexpensive method to assess gastric emptying it has not been universally accepted. This technique relies on rapid

absorption and metabolism of the Na $^{13}$C-acetate tracer to produce a detectable increase in $^{13}CO_2$ in exhaled breath. Pulmonary excretion of $^{13}$C as carbon dioxide may be dependent on its passage through the blood bicarbonate system, resulting in dilution and a breath signal that is delayed, blunted or reduced in comparison with gastric emptying (Sanaka et al, 2008). The Bluck and Coward formula applied in this chapter is self-correcting (Bluck et al, 2006) and accounts for the delay in appearance of $^{13}CO_2$ in exhaled breath, however, it assumes that the bicarbonate kinetics can be described using a single body pool. This system allows the whole of the gastric emptying profile to be generated and is directly comparable with scintigraphy.

The stable isotope breath test has not been widely applied in the postoperative period. Other techniques such as the paracetamol absorption have been applied (Avrahami et al, 1999), however, they did not appear to correlate with postoperative gastrointestinal symptoms such as PONV (Wattwil et al, 2002). Other techniques such as Magnetic resonance imaging or scintigraphy may be considered gold standards, however, they require greater inconvenience for the patient and are more expensive. These techniques will also be obstructive to the other postoperative elements of the ERAS programme.

Postoperative day 3 was chosen for the gastric emptying breath test as patients were scheduled to move from the high dependency unit to a standard ward environment on this day. This allowed easier patient access. Due to the pilot nature of this study there was not any data to compare the specific timing of this test. It would be useful in future studies to assess gastric emptying at different time points, especially earlier after surgery. Ideally multiple time points should be assessed. The stable isotope

breath testing would be particularly suited to this as it is possible to repeat the test on multiple occasions on the same individual and increasing the number of test would have a negligible effect on overall expense.

The stable isotope breath test is a feasible and economical method of measuring gastric emptying rate in the early postoperative period. This may provide a more objective measure of recovery and therefore be a more suitable endpoint in future ERAS studies. Further studies will be required to assess the relationship between gastric emptying rate and overall functional recovery, however, it would appear that an extremely delayed gastric emptying may be associated with a poorer tolerance of oral diet and a longer requirement of inpatient care.

## *Chapter 5. Development of physical activity monitoring as an outcome measure*

### 5.1 Background

Postoperative outcomes utilised in ERAS programmes often overlap as markers of recovery and markers of protocol compliance. These outcomes are often subjective and can be influenced by the direction of medical staff. Although it is expected that patients achieving these postoperative protocol goals are likely to be the same patients making a rapid recovery objective end points of recovery may provide more useful evidence on which to refine future ERAS protocols.

The previous chapter of this thesis has explored the potential role of postoperative gastric emptying, measured with stable isotope breath testing, as a novel, objective assessment of postoperative recovery. This chapter will explore the potential role of postoperative physical activity as measured with a patient worn electronic activity meter as another objective measure of recovery

Early postoperative mobilisation is a well-established component of any postoperative care programme (Fearon et al, 2005). Postoperative immobility contributes both to postoperative complications and a prolonged convalescence after major abdominal surgery. Spontaneous physical activity itself may be a surrogate marker of pain control, strength, functional performance and overall wellbeing (Dahele et al, 2007). It has become possible to accurately monitor spontaneous physical activity through a new generation of small accelerometer devices. These devices are capable of registering detailed aspects of activity including the duration of sitting and lying, time

standing, time walking, number of up and down transitions, step cadence and estimated energy expenditure providing an objective measure of postoperative function over a period of up to a week. This device may be specifically useful in the postoperative period and its results may be a more objective measure of actual postoperative function.

As part of the study presented in Chapter 8, patients undergoing hepatic resection were asked to wear a small lightweight activity meter (ActivPAL™) from postoperative day three to day nine, then for a second period of five consecutive days between postoperative days thirty and forty. The aims of this study were to assess the acceptability, feasibility and patient compliance of wearing such a device and explore the potential role of physical activity as an endpoint.

## 5.2 Patients and methods

Patients taking part in this study were asked to wear a compact and lightweight (35 x 53 x 7 mm and 20 g) accelerometer-based activity monitoring system (ActivPAL™). The ActivPAL™ system was attached to the anterior thigh region between two transparent medical dressings to waterproof the device. Patients were asked to wear the ActivPAL™ activity meter between postoperative days three and nine and for a further five days between postoperative days thirty and forty. Data was transferred by an USB interface to a computer and specific software (ActivPAL™ Professional version 5.8.2.3, Research Edition, ActivPAL™, Glasgow, UK) was used to analyse data, display the outcome variables listed above for each day of measurement and estimate energy expenditure. The meter analyses data on a second by second basis to generate an activity profile. The mean activity per day of recording (only complete 24h recording days were included) was calculated for all participants and used in subsequent analysis.

The change in activity level in the early and late postoperative periods was assessed by median daily step count. Median step count was compared with time to achieve discharge criteria, length of hospital stay and average step count in the later postoperative period. Discharge criteria: no requirement for IV fluids, no requirement for parenteral analgesia and able to perform activities of daily living independently.

## 5.3 Results

Between postoperative day three and nine following surgery, fifty patients participated in wearing an activity meter for at least five days. Twenty-one of the original fifty subjects wore the activity meter for a second period approximately thirty days after surgery. For the group wearing activity meters in the early postoperative period overall male to female ratio was 28:22 and the median (IQR) age was 62 (52,67) years. Forty-six patients (92 %) were treated for malignant disease and there were thirty-eight major and twelve minor resections (Table 5.1).

The median (IQR) number of steps taken per day rose from 299 (85,727) on postoperative day three to 1998 (1130,3062) on postoperative day nine (Fig 5.1). In the later postoperative phase of recovery there was a large day-to-day variation in median step count. The lowest median step count in this period was 2760 (2385.5,6023.5) and the highest 5723 (2152,10169) (Fig 5.2).

On postoperative day three patients achieving the greatest step count (>90th percentile) had a significantly shorter length of hospital stay compared with the rest of the patients. On the same day, patients with the lowest step count (<$10^{th}$ percentile) had a significantly longer length of hospital stay. There were no significant differences between the groups for time to achieve discharge criteria or activity rate in the one-month postoperative period. There was also no significant difference between the groups for extent of hepatic resection (Tables 5.2 – 5.5).

On postoperative day five patients achieving the greatest step count (>90th percentile) also had a significantly shorter length of hospital stay compared with the rest of the

patients but no significant differences between the groups for time to achieve discharge criteria or activity rate in the one-month postoperative period. However on postoperative day five patients with the lowest step count ($<10^{th}$ percentile) had a significantly longer time to achieve discharge criteria, a significantly longer length of hospital stay and a significantly lower activity level in the later postoperative period. There was no significant difference between the groups for extent of hepatic resection (Tables 5.6 – 5.9).

**Table 5.1. Overall demographics of 50 patients wearing ActivPAL™ activity meter in the early postoperative period (Days 3 – 9).**

| | Overall group n=50 |
|---|---|
| **Age (years)*** | 62 (52,67) |
| **Sex ratio (M:F)** | 28:22 |
| **ASA grade** | |
| **I** | 11 (22) |
| **II** | 33 (66) |
| **III** | 6 (12) |
| **Pathology** | |
| **Malignant** | 46 (92) |
| **Benign** | 4 (8) |
| **Extent of hepatic resection** | |
| **Major** | 38 (76) |
| **Minor** | 12 (24) |

Values in parentheses are percentages unless indicated otherwise; *values are median (interquartile range). ASA, American Society of Anesthesiologists.

**Fig 5.1: Step count between postoperative days 3 – 9 for patients wearing an ActivPAL™ activity meter.**

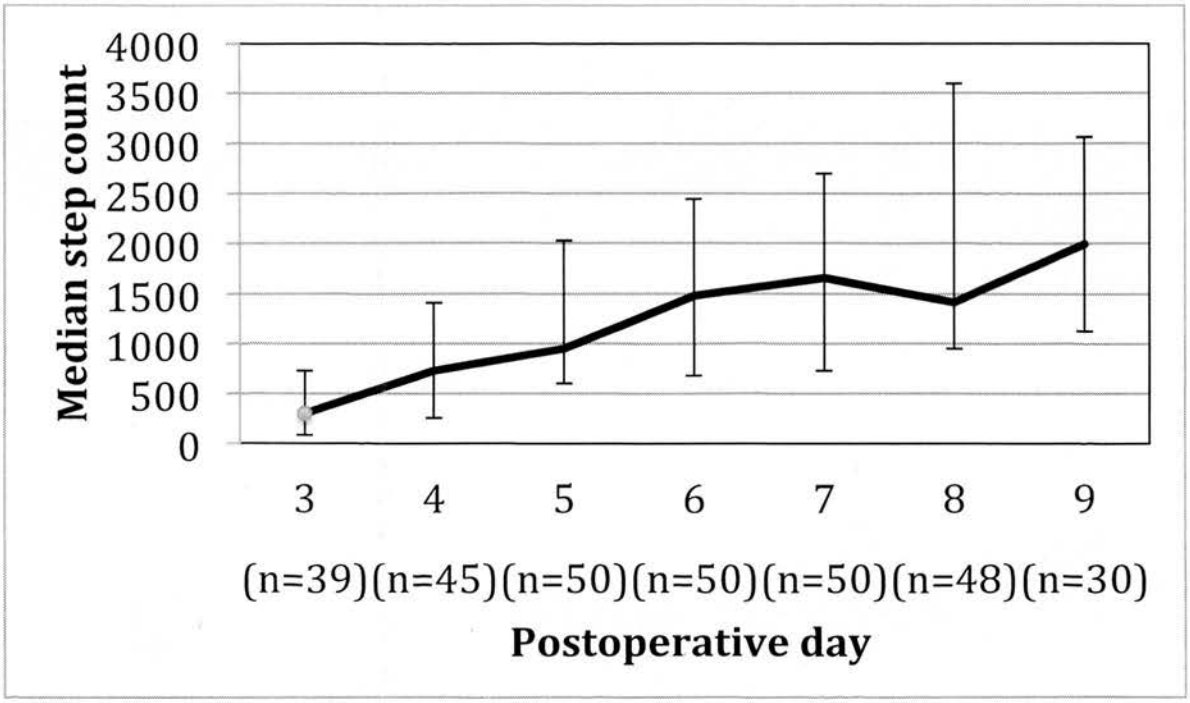



**Fig 5.2: Step count between postoperative days 30 - 40 for 21 patients wearing an ActivPAL™ activity meter.**

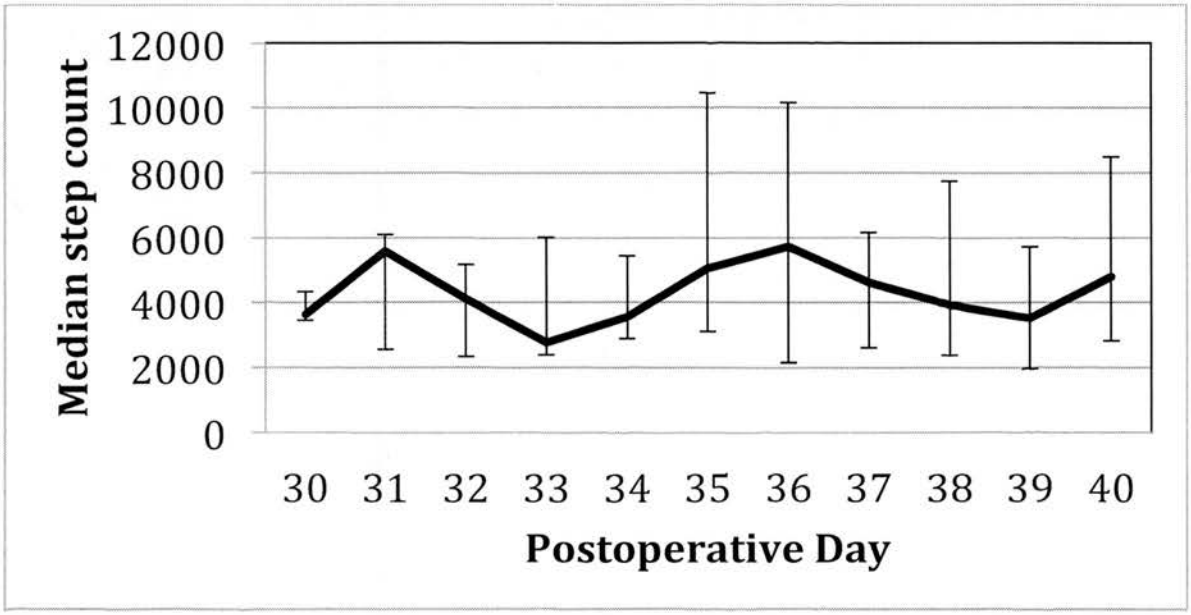


**Table 5.2. Comparison of postoperative outcomes for patients with significantly greater step count (>90$^{th}$ percentile) with patients with typical step count (<90$^{th}$ percentile) on postoperative day three.**

| | <90$^{th}$ percentile | >90$^{th}$ percentile | p |
|---|---|---|---|
| **Time to achieve DC criteria*** | 4 (4,5) | 3.5 (3,4) | 0.110‡ |
| **Length of stay*** | 6 (4,7) | 4 (4,4.75) | 0.037‡ |
| **Average step count in late period*** | 4923 (2175,6938) | 9003 (4130,11173) | 0.117‡ |

*Values are median (interquartile range). ‡Mann–Whitney U test.

**Table 5.3. Comparison of extent of liver resection for patients with significantly greater step count (>90$^{th}$ percentile) with patients with typical step count (<90$^{th}$ percentile) on postoperative day three.**

| | <90$^{th}$ percentile | >90$^{th}$ percentile | p* |
|---|---|---|---|
| **Minor resection** | 6 (16) | 1 (25) | |
| **Major resection** | 32 (84) | 3(75) | 0.532 |

Values in parentheses are percentages. *Fisher's exact test.

**Table 5.4. Comparison of postoperative outcomes for patients with significantly lower step count (<10 percentile) with patients with typical step count (>10$^{th}$ percentile) on postoperative day three.**

| | <10$^{th}$ percentile | >10$^{th}$ percentile | p |
|---|---|---|---|
| **Time to achieve DC criteria*** | 4.5 (4,7.25) | 4 (3,5) | 0.258‡ |
| **Length of stay*** | 8.5 (7.25,11.25) | 5 (4,6) | 0.008‡ |
| **Average step count in late period*** | 3900 (2093,5707) | 6076 (2857,8977) | 0.369‡ |

*Values are median (interquartile range). ‡Mann–Whitney U test.

**Table 5.5. Comparison of extent of liver resection for patients with significantly lower step count (<10$^{th}$ percentile) with patients with typical step count (>10$^{th}$ percentile) on postoperative day three.**

| | <10$^{th}$ percentile | >10$^{th}$ percentile | p* |
|---|---|---|---|
| **Minor resection** | 0 (0) | 7 (18) | |
| **Major resection** | 4 (100) | 31 (82) | 1.0 |

Values in parentheses are percentages. *Fisher's exact test.

**Table 5.6. Comparison of postoperative outcomes for patients with significantly greater step count (>90$^{th}$ percentile) and patients with typical step count (<90$^{th}$ percentile) on postoperative day five.**

| | <90$^{th}$ percentile | >90$^{th}$ percentile | P |
|---|---|---|---|
| **Time to achieve DC criteria*** | 4 (4,5) | 4 (3.5,5) | 0.849‡ |
| **Length of stay*** | 6 (4.25,7) | 4 (4,5) | 0.043‡ |
| **Average step count in late period*** | 5807 (2361,6967) | 7949 (5122,10663) | 0.126‡ |

*Values are median (interquartile range). ‡Mann–Whitney U test

**Table 5.7. Comparison of extent of liver resection for patients with significantly greater step count (>90$^{th}$ percentile) and patients with typical step count (<90$^{th}$ percentile) on postoperative day five.**

| | <90$^{th}$ percentile | >90$^{th}$ percentile | p* |
|---|---|---|---|
| **Minor resection** | 6 (17) | 1 (25) | |
| **Major resection** | 30 (83) | 3 (75) | 0.552 |

Values in parentheses are percentages. *Fisher's exact test.

**Table 5.8. Comparison of postoperative outcomes for patients with significantly greater step count (<10 percentile) and patients with typical step count (>10th percentile) on postoperative day five.**

| | <10th percentile | >10th percentile | |
|---|---|---|---|
| **Time to achieve DC criteria*** | 5 (4.5,8) | 4 (3.25,5) | 0.034‡ |
| **Length of stay*** | 10 (9,11.5) | 5 (4,6) | 0.001‡ |
| **Average step count in late period*** | 2964 (1393,5273) | 6637 (3738,7913) | 0.046‡ |

*Values are median (interquartile range). ‡Mann–Whitney U test

**Table 5.9. Comparison of extent of liver resection for patients with significantly greater step count (<10th percentile) and patients with typical step count (>10th percentile) on postoperative day five.**

| | <10th percentile | >10th percentile | p* |
|---|---|---|---|
| **Minor resection** | 0 (0) | 7 (19) | |
| **Major resection** | 4 (100) | 29 (81) | 1.0 |

Values in parentheses are percentages. *Fisher's exact test.

## 5.4 Discussion

In the present study 50 patients wore the activity meter in the early postoperative period without any reported difficulties. This demonstrates that a patient worn activity meter in the postoperative period is acceptable to patients.

As many of the patients lived remotely to the hospital meters were returned by prepaid, recorded delivery after recording the time and date of removal (this was usually apparent from the data analysis itself). This method of return did restrict the use of the meters (due to the number of meters available) and hence there were insufficient meters for all patients to record activity data for the second observation period at thirty days.

In the present protocol the activity meters were attached to the subjects by the author, as the meter required activation and careful attachment to the subject. Again as many of the subjects did not live locally to the hospital it was not possible for all subjects to attend the hospital for this purpose. In the period one-month post surgery only twenty-one of the original subjects wore the meter. This may present a problem with future studies. Although the meters can be programmed and switched off allowing the subject to attach the meters themselves this relies both on having additional meters available and on the patients being able to attach the meter after one demonstration. This risks data not being collected and potentially damage to the device itself if exposed to water.

The results presented in this chapter highlight the rapid rise in activity level during the early postoperative period. In the period one-month post surgery the trendline

suggests that despite day-to-day variation, median number of steps taken per day is no longer improving. This suggests that activity level one-month post surgery may be approaching its preoperative level. It may be difficult to draw any firm conclusions from the results in this later period as not all patients participated in this second phase of activity monitoring. Moreover, it was not possible to obtain activity levels prior to surgery for comparison.

The chapter also suggests that spontaneous activity level in the early postoperative period (day three or five) may predict length of hospital stay. Patients with a reduced step count ($<10^{th}$ percentile) on days three or five have a longer length of hospital stay and those with a higher step count ($>90^{th}$ percentile) have a shorter length of hospital stay. Patients with a reduced step count ($<10^{th}$ percentile) on postoperative day five also have a reduced activity level thirty days following surgery. The results in this study may simply be highlighting patients who are doing well or less well following surgery. However, this may allow a prediction of recovery rate very early in the postoperative period. It is also possible that motivated patients who mobilise more aggressively in the early postoperative period are improving their physical status enough to get home from hospital earlier and have an improved activity level approximately one month later. This would suggest that postoperative step count might be useful both as a marker of early postoperative recovery and a predictor of length hospital stay.

Previous studies have used wrist worn activity meters, which differentiate between periods of rest, sleep and movement and generate an activity score (Zutshi et al, 2004;King et al, 2006). These studies compared laparoscopic with open surgery.

Despite significant differences in postoperative outcomes such as length of hospital stay there was no difference in median postoperative activity score. The ActivPAL™ activity meter is able to record duration of sitting and lying, the time standing, the time walking, number of up and down transitions, step cadence and estimated energy expenditure. This study assessed step count as it was felt that this would be the best measure of spontaneous and intentional activity in the early postoperative period. In less mobile patients up/down transitions or time standing may be of use to differentiate patients with a lower activity level. As the ActivPAL™ activity meter is leg mounted it measures only activity involving the lower limbs. It may therefore underestimate energy expenditure from use of the upper limbs. In the present cohort of patients this was not likely to be significant. Other activity recording systems available include the Actireg® (Hustvedt et al, 2004) or the IDEEA® (Zhang et al, 2004). However, these systems require more hardware to be worn and may be more restrictive to patients.

The time periods selected for assessment were arbitrary, however, day three was when patients were scheduled to leave the high dependency unit. Prior to this day patients were not able to leave the high dependency unit unescorted. There was not any existing evidence on which to base selection of a particular time period for assessment. In the present pilot study it was not feasible to gather preoperative activity data due to the short notice at which surgery was often scheduled and the distance that most patients had to travel from home, which was prohibitive to additional hospital visits. In future studies it may be useful to compare postoperative activity level with preoperative level, which will demonstrate the time to recovery of preoperative activity level.

The ActivPAL™ activity monitor is small and unobtrusive, it was tolerated by all of the patients who wore it and did not hinder any of their normal activities. The use of the transparent medical dressings allowed the device to be partially waterproofed and able to withstand showering. Subjects wearing the device were asked not to submerge the device in water, which precluded bathing.

The study presented in this chapter suggests that objective measurement of postoperative activity level with a patient worn activity meter is feasible. The results presented here provide a snapshot of postoperative activity level, which appears to correlate with other markers of postoperative recovery. Although, due to their exploratory nature, the results here have to be reviewed with caution, there appears to be sufficient evidence to support further interest.

# SECTION E. PRECONDITIONING REGIMENS FOR ERAS

Within many existing ERAS programmes, preoperative metabolic conditioning with a carbohydrate rich beverage plays a prominent role. Carbohydrate and fluid loading has been demonstrated to reduce preoperative thirst, hunger and anxiety (Hausel et al, 2001) and postoperative nausea (Hausel et al, 2005). Postoperative insulin resistance is reduced (Soop et al, 2001) which maintains patients in an anabolic state, reducing protein loss (Svanfeldt et al, 2007) and maintaining both muscle mass (Yuill et al, 2005) and muscle strength. It is also suggested that use of a carbohydrate and fluid loading in colorectal surgery may be linked with an accelerated recovery and shorter length of hospital stay (Nygren et al, 2001;Noblett et al, 2006). In the first chapter of this section the feasibility and safety of applying such a carbohydrate rich beverage within the context of active mechanical bowel preparation is explored. In the second chapter of this section, the safety of administering a more complex pre-conditioning regimen containing glutamine and antioxidants (as well as carbohydrate) is explored in relation the need for complete gastric emptying immediately prior to surgery.

## *Chapter 6. Combination of mechanical bowel preparation with fluid and carbohydrate loading within the ERAS protocol*

### 6.1 Background

As previously stated in this thesis, preoperative oral carbohydrate (CHO) and fluid loading is a common component of enhanced recovery programmes. It has been shown to maintain postoperative nutritional status by reducing postoperative insulin resistance (Nygren et al, 1998;Soop et al, 2001), reduce nitrogen loss and aid overall postoperative recovery (Nygren et al, 2001;Yuill et al, 2005;Noblett et al, 2006). Within the context of traditional perioperative care, administration of oral nutritional supplements in the preoperative period has been shown to maintain perioperative nutritional status and reduce postoperative weight loss (Smedley et al, 2004). Oral or enteral nutritional support administered in the early postoperative period has been shown to reduce both infectious complications and length of hospital stay (Lewis et al, 2001;Andersen et al, 2006). Use of preoperative CHO loading to reduce postoperative insulin resistance may further optimise the benefits of such early postoperative feeding.

Traditional periods of preoperative fasting beyond that recommended by National Anaesthesia Societies and recent meta-analysis (Brady et al, 2003) are still prevalent (Hannemann et al, 2006) and are often prolonged due to the concomitant use of mechanical bowel preparation (MBP). Prolonged fasting decreases the capacity to cope with the surgical stress response, increases postoperative insulin resistance and may affect adversely length of stay (Thorell et al, 1999). Such fasting may also further compromise the fluid and electrolyte balance of patients receiving mechanical bowel preparation (Rothman et al, 1991).

Although it has been demonstrated that routine mechanical bowel preparation has no proven benefit in relation to anastomotic leak rate following colonic resection there are still incidences where it may be of benefit (Guenaga et al, 2009). Bowel preparation may aid in the identification of small tumours, will allow on table colonoscopy and would seem appropriate if a defunctioning ileostomy is to be created. The situation is less clear for patients undergoing rectal resection. Although the incidence of symptomatic anastomotic leaks was similar in the absence of mechanical bowel preparation there was more significant pelvic sepsis associated with a leak (Bretagnol et al, 2007). In general the use of MBP in colorectal surgery is still relatively common (Nygren et al, 2005) and often directed by surgical preference (Lassen et al, 2005). In the present study Oral Nutritional supplements were administered the day before surgery in place of solid food (which would be precluded with MBP).

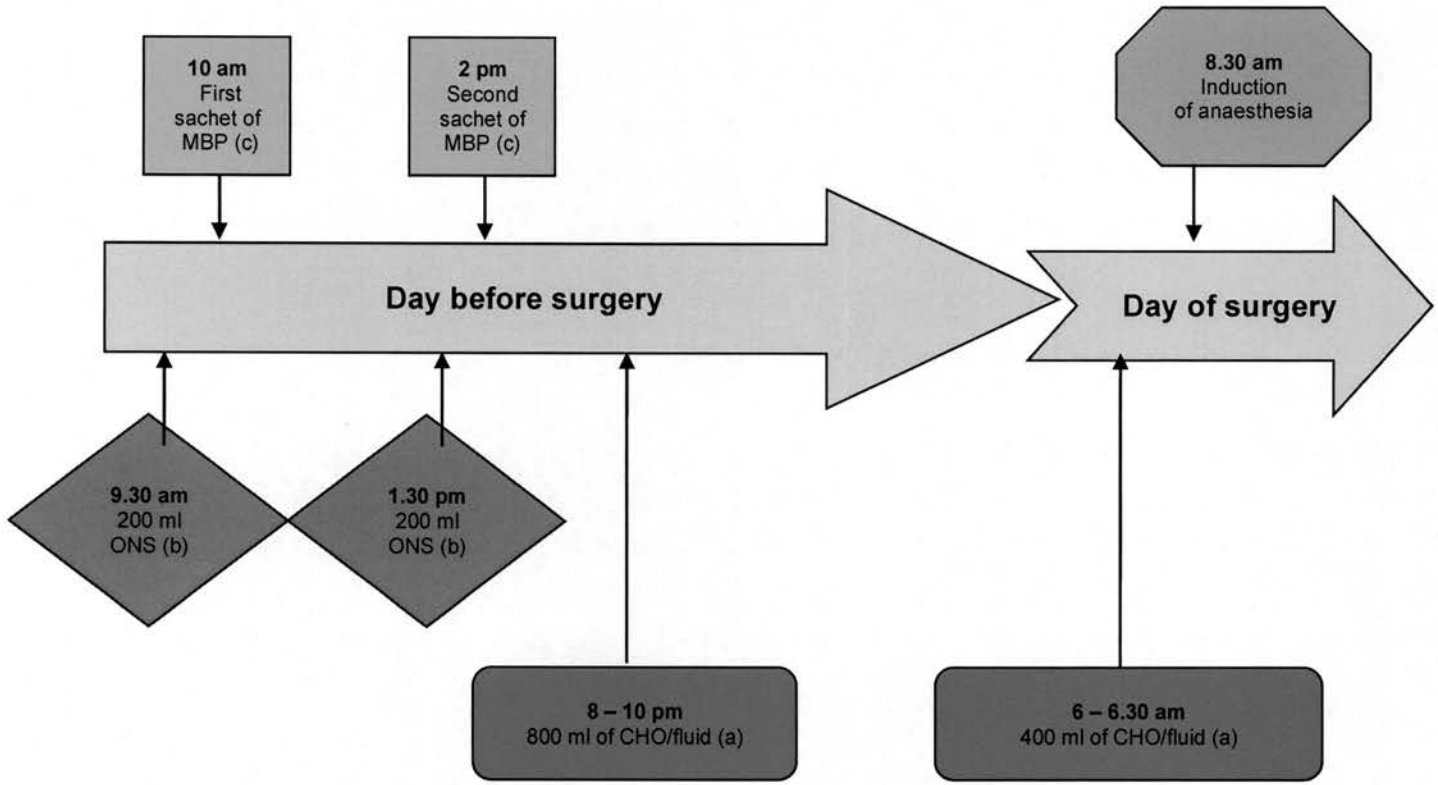
Although pre-operative fasting for six hours is required for solids, it is accepted that clear fluids should be encouraged up to two hours prior to surgery (Brady et al, 2003;Ljungqvist et al, 2003). Specially designed polymeric CHO beverages can also be administered up to two hours prior to surgery as they have been demonstrated to empty from the stomach within 90 minutes (Nygren et al, 1995) and as glucose absorption occurs rapidly in the upper gastrointestinal tract and is unaffected by administered prokinetic agents (Brunetto et al, 1990) it is unlikely to be affected by MBP.

This aim of this chapter is to demonstrate that patients can comply with routine preoperative conditioning with oral nutritional supplements, an oral carbohydrate solution and mechanical bowel preparation prior to elective left colonic or rectal resection.

## 6.2 Patients and methods

This study was conducted in the colorectal unit at the Western General Hospital in Edinburgh, UK. Ethical approval was obtained from Lothian Research Ethics committee and written consent obtained from each patient after verbal and written information had been provided in a clinic visit prior to admission. Patients undergoing elective left colonic or rectal resection for benign or malignant disease were recruited and were prescribed preoperative MBP (2 sachets of Picolax®). Patients followed an Enhanced Recovery After Surgery protocol as previously described (Fearon et al, 2005). As part of the ERAS protocol the ERAS research nurse either provided the drinks / instructions at the preadmission clinic or for inpatients requested that the surgical house officer prescribed the following regimen on the patients drug chart: 200 ml of an Oral Nutritional Supplement (ONS: Fortijuice®, Nutricia) prior to the first sachet of bowel preparation and another 200 ml of ONS prior the second sachet of bowel preparation. Non-diabetic patients were prescribed oral CHO/fluid as 400-800 ml of a 12.5% clear beverage (Nutricia Preop®) at 8 pm the evening before surgery and a further 400 ml 2 - 3 hour before surgery (Fig 6.1). Compliance with the protocol was audited prospectively.

**Fig 6.1 Protocol for administration of preoperative carbohydrate and fluid loading / Oral Nutritional supplements in combination with mechanical bowel preparation prior to left sided colonic and rectal resection.**

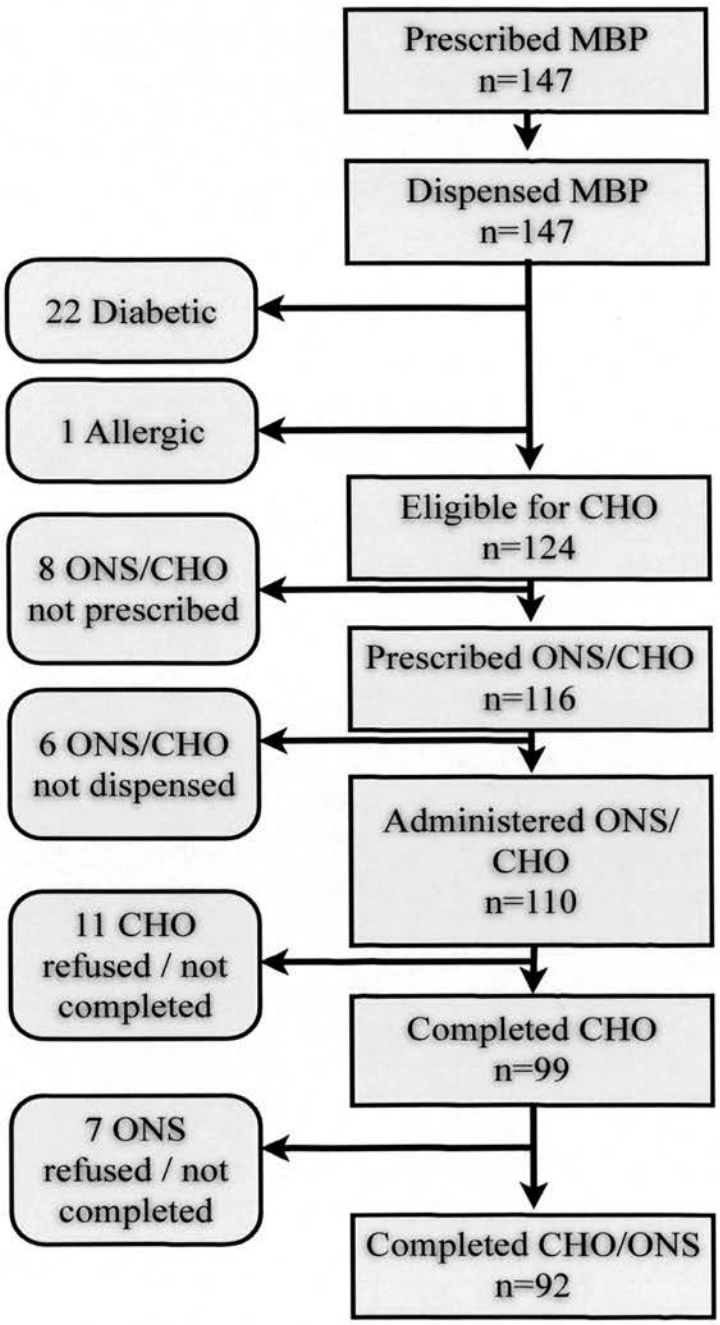



(a) CHO/fluid :Carbohydrate and fluid loading (Preop®, Nutricia)
(b) ONS : Oral nutritional supplement (Fortijuice®, Nutricia)
(c) MBP: Mechanical Bowel Preparation (Picolax®)

## 6.3 Results

Between March 2002 and April 2006 one hundred and forty seven patients underwent elective left colonic (n=42) or rectal resection (n=105) within an ERAS programme of care but received MBP. There were 70 males and 77 females. Mean (sd) age was 64 (14.2). Twenty-two patients were diabetic and therefore not eligible to receive preoperative CHO/fluid loading. One patient did not receive the CHO loading due to an allergy to lemon-flavoured drinks. There were 124 patients eligible to undertake the protocol. The protocol failed in 14 patients (eight regimen not prescribed by the medical staff, six regimen not dispensed by the nursing staff). Of the patients that were eligible to undertake the protocol, 99 (80 %) completed the prescribed volume of CHO / fluid loading with no adverse effects. Eleven patients did not complete the CHO drinks, seven patients did not tolerate them, two refused to try them, one patient vomited and in one case the reason was not recorded. 103 (83 %) completed the full-prescribed volume of ONS and 92 patients completed the combined regimen of ONS and CHO drinks. In summary, 92 (74 %) of 124 patients that were eligible tolerated the drinks and completed the regimen (Fig 6.2).

**Fig 6.2 Consort diagram for 147 patients receiving preoperative oral fluid/carbohydrate loading and oral nutritional supplements in conjunction with MBP prior to elective left colonic or rectal resection.**




CHO: Carbohydrate and fluid loading (Preop®, Nutricia)
ONS: Oral nutritional supplement (Fortisip®, Nutricia)

## 6.4 Discussion

The study presented in this chapter demonstrates that 84 % of patients completed and tolerated preoperative oral fluid / CHO loading and ONS in conjunction with MBP prior to elective left colonic or rectal resection. A previous study by Tjandra and colleagues examined oral CHO / electrolyte replacement in conjunction with MBP prior to colonoscopy and demonstrated a similar level of tolerance (Tjandra et al, 2004). Taken together, these findings suggest it is feasible to prescribe simultaneous MBP and CHO / fluid loading and that patients will comply well with both regimens. Interestingly, a recent study by Noblett and co-workers examining the role of preoperative CHO / fluid loading demonstrated a high level of patient compliance and earlier functional recovery following colorectal surgery. It was not clear whether patients had received concomitant MBP in the study (Noblett et al, 2006).

The protocol used in our study was designed to account for the fact that during MBP patients cannot eat solid food and require extra oral fluids to counteract dehydration. Recent evidence from Ljungqvist and co-workers (the group that originally demonstrated the benefits of preoperative oral CHO/fluid loading) has shown that 400 ml oral CHO / fluid loading 2 hours prior to induction of anaesthesia is sufficient to reduce postoperative insulin resistance if the patient takes normal food until 10 pm on the previous day. The 800 ml oral CHO / fluid loading the evening before surgery does not add to the improved metabolic status and decreased postoperative insulin resistance (Svanfeldt et al, 2005). In the light of these recent findings it might be possible to omit the CHO / fluid loading at 8-10 pm the night before surgery and replace this with further ONS (as MBP would preclude solid food).

In this study approximately 15% of all patients were 'ineligible' for oral CHO loading due to the presence of diabetes. Diabetes is, however, only a relative contra-indication (Gustafsson et al, 2008). A second issue raised by the present study is that of protocol failure. Clearly the present regimen represents a more complex form of preoperative preparation than simply starving the patient for 12 hours. Protocol failure (11 %) was due either to failure to prescribe the regimen or failure to dispense the regimen. This occurred almost exclusively in those patients who received MBP as inpatients. Clearly similar issues are more easily avoided in patients prepared at home and admitted on the same day as surgery.

The haemodynamic and metabolic benefits of preoperative carbohydrate and fluid loading are clear and should not be denied to patients receiving mechanical bowel preparation. From the present study it is apparent that with a clearly defined protocol patients undergoing MBP are capable of completing a regimen of CHO / fluid loading combined with ONS prior to surgery.

## *Chapter 7. Safety evaluation (gastric emptying) of a novel nutritional preconditioning regimen in healthy volunteers*

### 7.1 Background

Enhanced Recovery After Surgery programmes have dramatically improved the speed of postoperative recovery and reduced postoperative morbidity (Fearon et al, 2005;Wind et al, 2006). Within these programmes patients are encouraged to take clear fluids up until two hours before anaesthesia and up to six hours before solid food, in keeping with modern anaesthetic guidelines (American Society of Anesthesiologists, 1999;Brady et al, 2003;Søreide et al, 2006;Woods et al, 2007). Preoperative metabolic conditioning with 400 ml of a clear carbohydrate drink (CCD) two hours before the induction of anaesthesia, has been shown to reduce; postoperative insulin resistance, postoperative nausea and vomiting, preoperative discomfort and anxiety, and to improve patient wellbeing (Nygren et al, 1995;Hausel et al, 2001;Nygren, 2006). Data from a randomised trial suggests that preoperative carbohydrate loading in patients undergoing colorectal surgery results in a shorter length of hospital stay (Noblett et al, 2006). This volume of CCD empties completely from the stomach within 90 minutes and therefore does not increase aspiration risk during induction of anaesthesia (Nygren et al, 1995). One currently available CCD, [Nutricia preOp® (Nutricia Clinical Care, Trowbridge, UK)], has already been shown to be safe in a large number of patients undergoing major abdominal surgery (Nygren et al, 1995;Yuill et al, 2005;Breuer et al, 2006;Noblett et al, 2006).

Following surgery there is a well-recognised period of insulin resistance similar to non-insulin dependent diabetes mellitus (Thorell et al, 1999). During this period

despite elevated levels of insulin there is decreased glucose uptake in skeletal and adipose tissue and increased glucose release. Administration of 400 ml of clear liquid containing 50 g of complex carbohydrate, such as Nutricia Preop®, stimulates an endogenous insulin release that is comparable to insulin release following a mixed meal (McMahon et al, 1989). This carbohydrate load increases the action of insulin by about 50 % three hours after ingestion and the enhanced action of this insulin surge at the onset of anaesthesia is likely to explain the postoperative effect on insulin resistance (Svanfeldt et al, 2005). Postoperative insulin resistance is attenuated, and both glucose disposal in peripheral tissues and oxidative glucose metabolism are improved. Overall insulin resistance is reduced by 50 % on postoperative day 1 (Soop et al, 2001).

The use of additional metabolic conditioning agents such as glutamine and antioxidants may be of further benefit to patients undergoing major abdominal surgery. Glutamine is a conditionally essential amino acid, which improves both gastrointestinal perfusion and immune function (Roth, 2008). Glutamine and antioxidant supplementation has been demonstrated to improve morbidity and survival in critically ill patients (Houdijk et al, 1998;Jones et al, 1999;Déchelotte et al, 2006;Berger et al, 2007). When used in major gastrointestinal surgery it may modulate the immune-inflammatory response (van Stijn et al, 2010), reducing postoperative complications and length of hospital stay (Beale et al, 1999;Heys et al, 1999;Heyland et al, 2001;Montejo et al, 2003). These benefits have been demonstrated in both undernourished (Braga et al, 2002) and well nourished gastric cancer patients (Braga et al, 2002;Gianotti et al, 2002) and its role is promoted in ESPEN guidelines (Weimann et al, 2006). When used in combination with

carbohydrate loading glutamine may also reduce oxidative stress (Awad et al, 2010).

A new product containing glutamine and antioxidants in addition to carbohydrate [Oral Nutrition Supplement (ONS), Fresenius Kabi, Bad Homburg, Germany] may, therefore, provide additional benefits for patients undergoing major abdominal surgery. However, as gastric emptying is affected by volume, nutrient content, viscosity (Marciani et al, 2001) and osmolality (Horowitz et al, 1994) the time taken for this beverage to empty from the stomach and, therefore, the safe time frame for preoperative administration, is not known.

Measurements of gastric emptying have been employed to study gastrointestinal function in a number of conditions, but results may differ according to the methodology (Lin et al, 2005;Bratten et al, 2006). Scintigraphic techniques have been regarded as the benchmark for such studies, but magnetic resonance imaging (MRI) is now becoming increasingly available and may be a more versatile option (Schwizer et al, 1992;Boulby et al, 1997;Feinle et al, 1999).

In the study presented in this chapter MRI was used to compare the gastric emptying times of two different types of preoperative metabolic conditioning drinks [ONS (Fresenius Kabi, Bad Homburg, Germany) and CCD (Nutricia preOp® (Nutricia Clinical Care, Trowbridge, UK))] in healthy volunteers. As the gastric emptying of 400 ml CCD has been determined previously using scintigraphy (Nygren et al, 1995), we compared identical volumes (400 ml) of the two drinks with the recommended dose of administration of ONS (300 ml).

## 7.2 Patients and methods

This was a randomised, double blind, three-way crossover study on healthy adult volunteers and was approved by the University of Nottingham Medical School Research Ethics Committee (approval K/5/2007). Informed written consent was obtained from all volunteers prior to enrolment and a system to report adverse events was in place.

Twenty healthy adult volunteers (10 male and 10 female, aged 18–45 years) were studied. All were suitable for MRI scanning (e.g. no metal implants in the body), had a normal body mass index (20–26 kg/ $m^2$) and no previous abdominal surgery or gastrointestinal disorders. Female volunteers were included only if they were not pregnant. A medical questionnaire was administered and a clinical examination performed prior to recruitment. Any volunteer who wished to withdraw from the study was entitled to do so at any time without giving a reason.

Each volunteer was randomised in a crossover manner to ingest 400 ml of a clear carbohydrate drink ((Nutricia preOp®) 50 g carbohydrate, 0 g protein) (CCD), 70 g ONS (50 g carbohydrate and 15 g glutamine) dissolved in water to a total volume of 400 ml (ONS400) and 70 g ONS dissolved in water to a total volume of 300 ml (ONS300). Volunteers reported for the studies at 0830 h after an overnight fast, on three separate occasions, each 7 days apart. They were instructed to abstain from alcohol and medications for 24h, and caffeine and strenuous exercise for 18 h. Baseline measurements included height, weight, body mass index and a fasting MRI scan.

The constituents and physical properties of the three test drinks are listed in Table 7.1. The drinks were reconstituted on the morning of each study and placed into identical opaque plastic bottles by a person not involved in the study. Volunteers were asked to ingest the drink from the bottle within 5 minutes and the time at which the drink was completed defined the zero time point.

**Table 7.1 Composition of three preoperative conditioning preparations tested in 20 healthy volunteers.**

| | CCD<br><br>(400 ml Nutricia preOp®) | ONS400<br><br>(70g oral nutritional supplement dissolved in water to a total volume of 400 ml) | ONS300<br><br>(70g oral nutritional supplement dissolved in water to a total volume of 300 ml) |
|---|---|---|---|
| Carbohydrate | | | |
| Maltodextrin/ saccharose/ modified starch/ gum arabic | | 50g | 50g |
| Maltodextrin/ fructose | 50.4g | | |
| **Glutamine** | | **15g** | **15g** |
| Vitamin C | | 750mg | 750mg |
| Vitamin E | | 250mg | 250mg |
| Green tea extract | | 1g | 1g |
| ß Carotene | | 5mg | 5mg |
| Zinc | | 10mg | 10mg |
| Selenium | | 150µg | 150µg |
| Energy | 200 kcal (836kj) | 234 kcal (978 kj) | 234 kcal (978 kj) |
| Dry matter content | 11.3% | 16.3% | 21.8% |
| pH | 4.9 | 3.9 | 3.9 |
| Density | 1.049 g/ml | 1.06 g/ml | 1.079 g/ml |
| Viscosity [at $\gamma$=1(1/s)] | 2.30m/Pa | 180 mPa | 627 mPa |
| Osmolarity | 228mOsm/kg | 508 mOsm/kg | 698 mOsm/kg |

MRI scanning was performed on a 1.5 T Philips Achieva scanner (Philips Healthcare, Eindhoven, The Netherlands) at the University of Nottingham). Each volunteer was positioned supine in the scanner with a sensitivity encoding (SENSE) body coil wrapped around the abdomen. First, a coarse, scout scan was performed to locate the position of the abdominal organs and position of the image planes followed by a calibration scan allowing automatic setup of the scanner specific to the volunteer. To assess gastric emptying a balanced turbo field echo (BTFE) imaging sequence was used to acquire 40 transverse (perpendicular to the longitudinal axis of the body) images with acquired planar resolutions of 2.50 mm x 1.56 mm (reconstructed to 1.56 mm x 1.56 mm) and slice thickness of 10 mm. This BTFE sequence (TR = 2.4 ms, TE = 1.19 ms, flip angle 45°) visualises fluid containing structures (hydrated test meals) with bright contrast against the surrounding organs. Each image set was acquired during a breath-hold of 17.6 seconds. MRI scans were performed in the fasted state (baseline), immediately after ingesting the drink (time 0), and then at 20-minute intervals until the stomach was empty.

The data set from each time point was recalled on a UNIX workstation and viewed to locate the gastric lumen and its contents. An example of a series through the abdomen of one subject is shown in Figs. 7.1. On such transverse sections, Analyze 6 (Biomedical Imaging Resources, Mayo Clinic, Rochester, MN) was used to trace manually around the region of interest (ROI) of the gastric contents on each slice. After this the volume of the gastric contents at each time point was calculated by summing across all ROIs. The totals for each time point were then tabulated and plotted onto spreadsheets in Microsoft Excel (Microsoft Corporation) to determine the gastric emptying kinetics. Individual gastric emptying curves were fitted on Microsoft

Excel to calculate the gastric half emptying time, T50. The volume remaining in the stomach at t = 60, 120 and 180 min were measured using MRI to assess complete gastric emptying.

The primary end point of the study was time to half gastric emptying (T50) of the three test drinks as measured by MRI. Secondary end points were residual gastric volumes at 60, 120 and 180 minutes Based on pilot scans, we anticipated a mean difference in T50 gastric emptying time of 30 minutes with a standard deviation of 30 minutes between CCD and ONS400. Assuming an $\alpha$ error of 0.01 and a power of 90%, the sample size was calculated to be 18. We recruited 20 subjects, making allowance for a 10 % drop out rate.

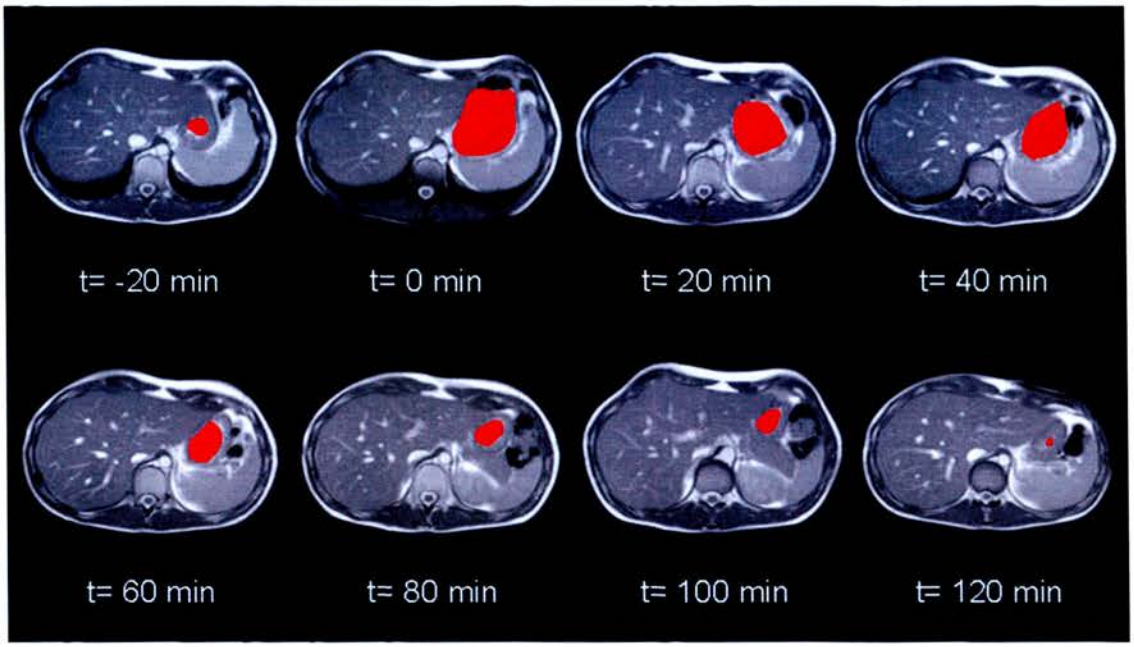
The order of administration of the three test drinks was determined using a web-based random number generator (http://www.randomizer.org/). Allocations were then concealed in sequentially numbered sealed opaque envelopes in triplicate, and were opened before each leg of the study by a person not involved in the study. That person then reconstituted the drinks and transferred them to opaque bottles before handing them to the investigators. Both the subjects and the investigators were blinded to group allocation. The randomisation code was broken after completion of the statistical analysis.

**Statistical analysis**

As the data were distributed normally, all results were expressed as mean (95% CI) or mean (SE). Differences between groups were tested for significance using the Student t-test (paired and unpaired), and were considered significant at $P < 0.05$. Statistical

analysis was performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA) and graphs were plotted on Microsoft Excel.

**Fig 7.1 Sequential axial MRI scans in one subject before and after ingestion of test drink with gastric content highlighted**



## 7.3 Results

The mean (SE) age, weight, height and body mass index (BMI) of the 20 volunteers were 29.4 (1.7) years, 68.1 (2.1) kg, 1.70 (0.02) m and 23.4 (0.4) km/m$^2$ respectively. Corresponding values for the 10 male volunteers were 33.0 (2.5) years, 75.3 (2.3) kg, 1.74 (0.03) m and 24.7 (0.3) km/m$^2$ and for the 10 female volunteers 25.8 (2.0) years, 60.8 (1.4) kg, 1.66 (0.02) m and 22.1 (0.6) km/m$^2$. All subjects completed the three arms of the study. One subject experienced mild nausea after ingesting ONS300, but there were no other side effects. Residual gastric volume, as measured by MRI, after an overnight fast, ranged from 0 to 95 ml (Table 7.2).

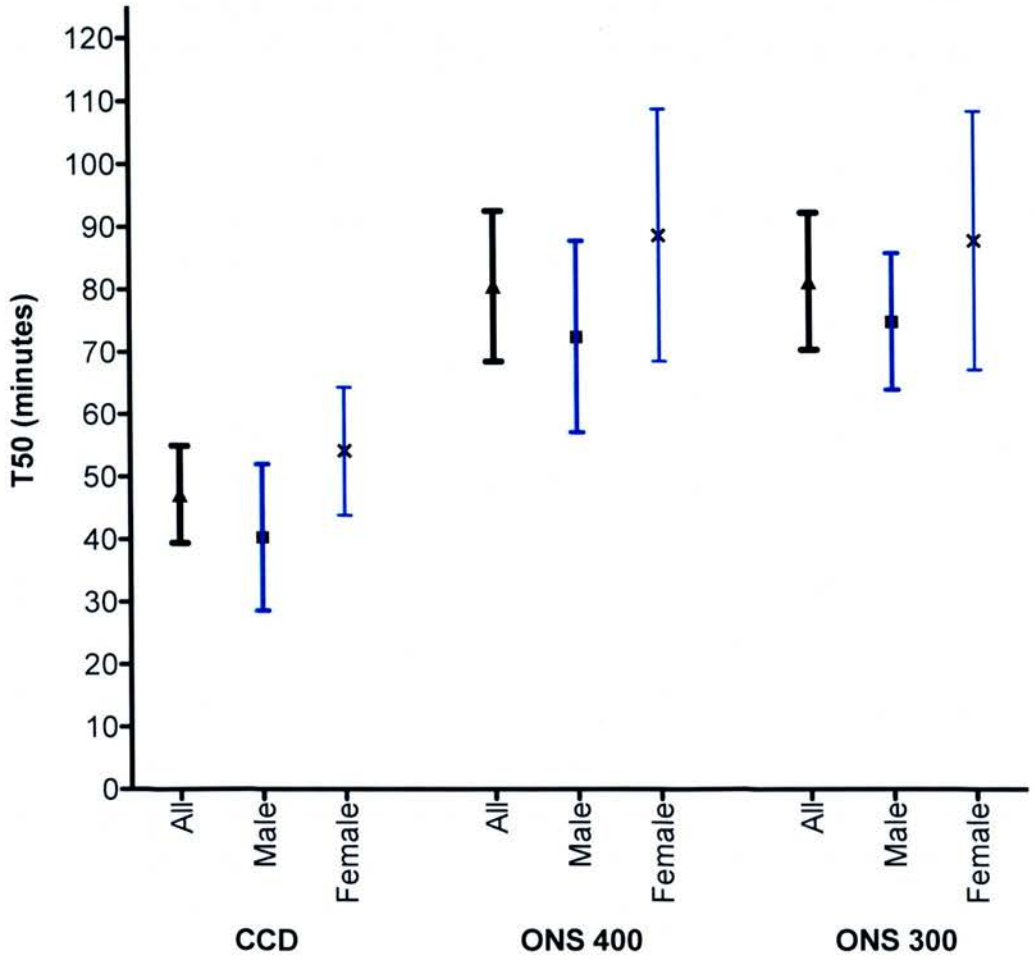
Mean (95% CI) T50 gastric emptying times were significantly lower ($p < 0.001$) with CCD, being 47 (39–55) min compared with 81 (69–93) and 81 (70–92) min for ONS400 and ONS300 respectively. Although T50 gastric emptying times were respectively longer in females than males, these differences were not statistically significant (Fig 7.2). The residual gastric volumes at 60, 120 and 180 minutes are shown in Figs. 7.3 - 7.5. At 120 minutes, the residual volume for CCD was not significantly different to the fasting residual volume ($p = 0.33$). At 120 minutes the residual volumes of ONS400 and ONS300 were significantly greater than there equivalent fasting residual volumes ($p < 0.001$) and ($p = 0.004$) respectively. The residual volumes of ONS400 and ONS300 had returned to baseline by 180 minutes (Fig 7.6).

**Table 7.2 Fasting residual gastric volumes for 10 male and 10 female subjects prior to receiving three different metabolic conditioning preparations.**

| | All Subjects (n=20) | Male Subjects (n=10) | Female Subjects (n=10) |
|---|---|---|---|
| Before CCD (400 ml Nutricia preOp®) | 21 (12-30) | 21 (6-35) | 21 (7-35) |
| Before ONS400 [70 g Oral Nutrition Solution dissolved in water to a total volume of 400 ml] | 29 (17-41) | 27 (7-47) | 31 (12-49) |
| Before ONS300 [70 g Oral Nutrition Solution dissolved in water to a total volume of 400 ml] | 32 (22-42) | 34 (23-46) | 30 (11-49) |
| Total | 27 (21-33) | 28 (19-36) | 27 (18-36) |

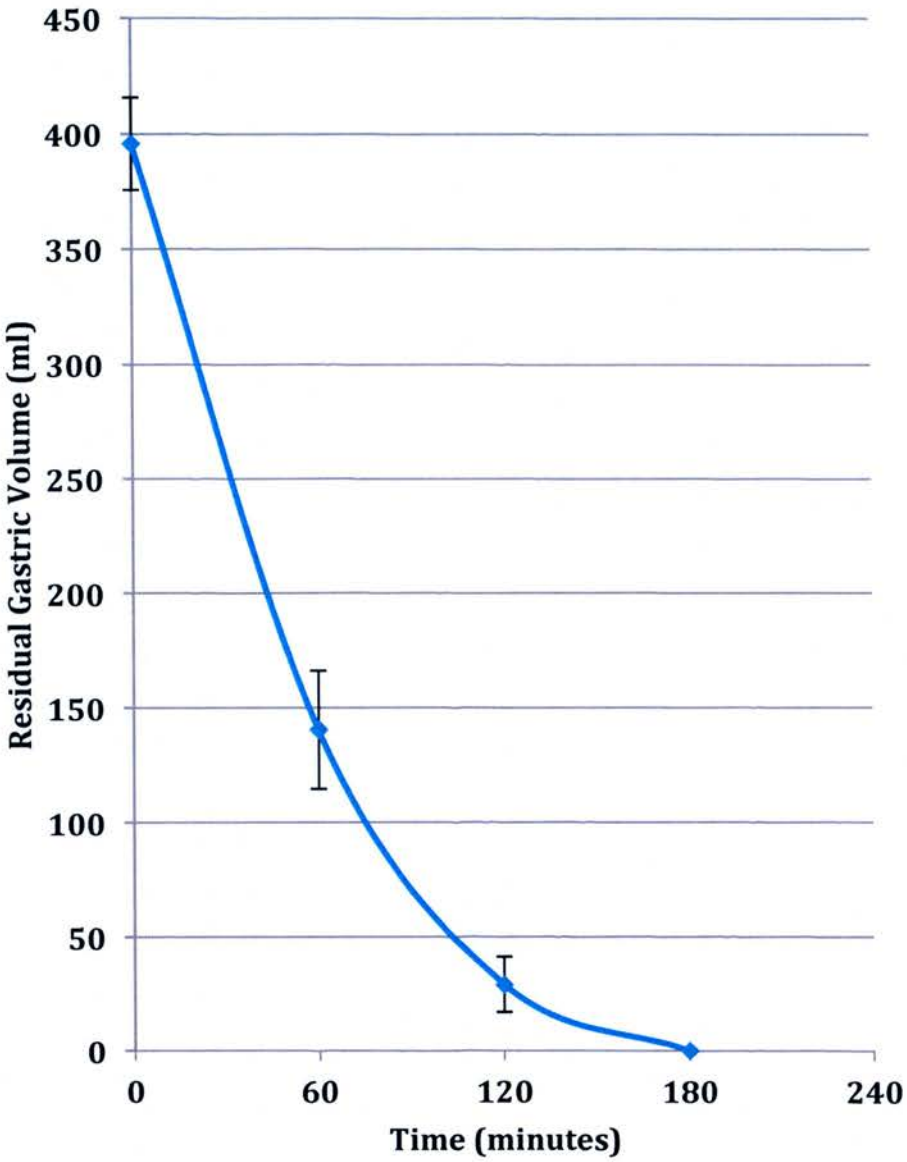
All values are mean (95% CI) ml. None of the differences were statistically significant.

**Fig 7.2 $T_{50}$ Gastric emptying time of 10 male and 10 female subjects given three different carbohydrate rich, metabolic conditioning preparations.**



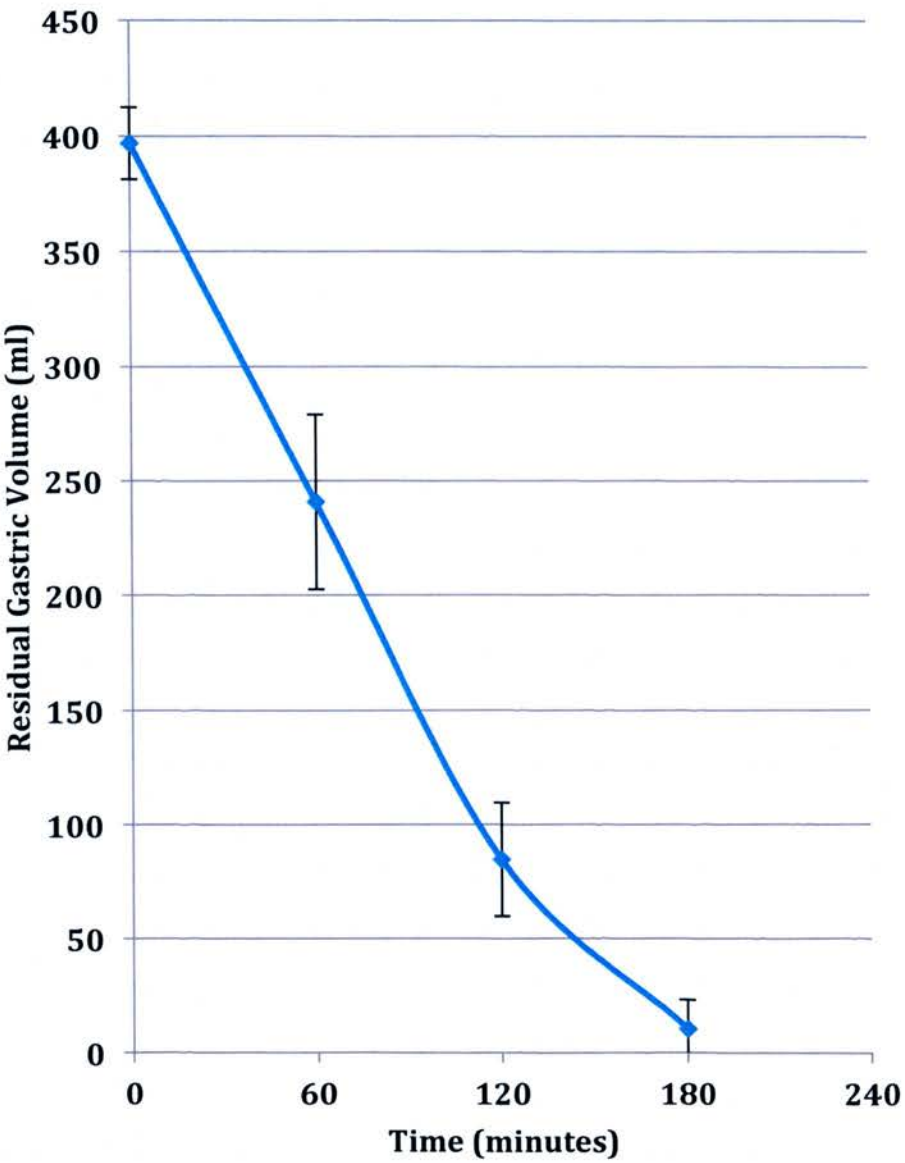

All values are mean (95% CI) minutes.

**Fig 7.3 Mean gastric residual Gastric Volume at 0, 60, 120, 180 for 20 patients given a 400 ml clear carbohydrate drink with 50.4g of maltodextrin (CCD)**



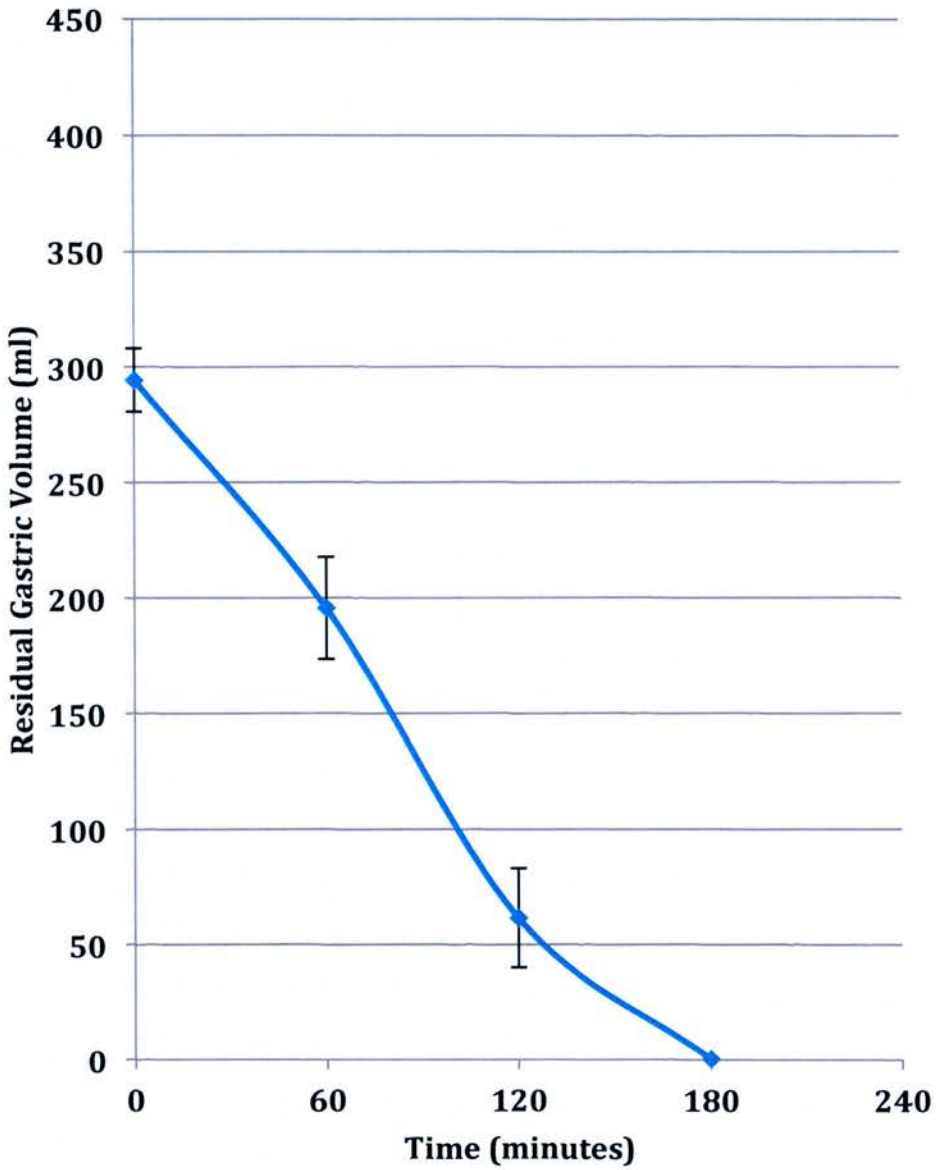

All values are mean (95% CI).

**Fig 7.4 Mean gastric residual Gastric Volume at 0, 60, 120, 180 for 20 patients given a 400 ml carbohydrate drink with 50g of maltodextrin ad 15g of glutamine (ONS400)**



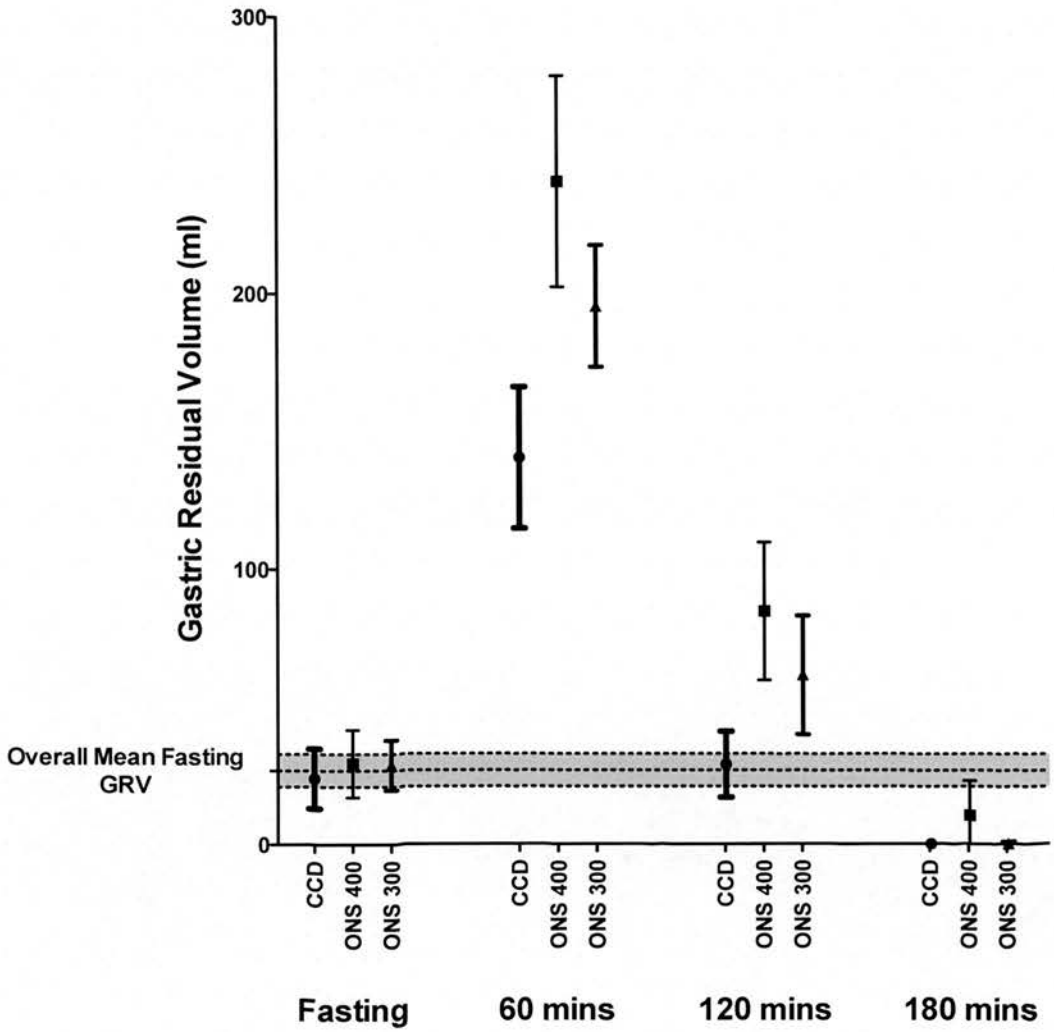

All values are mean (95% CI).

**Fig 7.5 Mean gastric residual Gastric Volume at 0, 60, 120, 180 for 20 patients given a 300 ml carbohydrate drink with 50g of maltodextrin and 15g glutamine (ONS300 drink)**




All values are mean (95% CI)

**Fig 7.6 Comparison of return to fasting gastric residual volume after administration of three different carbohydrate rich, metabolic conditioning preparations in 20 healthy volunteers**




All values are mean (95% CI)

## 7.4 Discussion

The study presented in this chapter confirms earlier work that a clear, carbohydrate rich drink will completely empty from the stomach in about 90 minutes (Nygren et al, 1995) and further supports guidelines that promote the administration of carbohydrates rich, clear fluids up to two hours before the induction of anaesthesia (Brady et al, 2003;Søreide et al, 2006;Woods et al, 2007). More complex liquid suspensions containing carbohydrate and amino acids, however, cannot be safely administered in the same time frame, as it would require up to three hours to empty form the stomach. This study also demonstrates that even after an overnight fast, the stomach is never completely empty. The residual volume in healthy volunteers can range from 0 to 95 ml with a mean of 27 ml as demonstrated with MRI.

With regard to the different metabolic conditioning preparations the CCD, which is a clear solution and contains no fat or protein, emptied at a significantly quicker rate than ONS400 and ONS300, which were suspensions. Despite the difference in volume, osmolarity, viscosity and density, the rates of emptying of the ONS400 and ONS300 drinks were similar. These findings suggest that the gastric emptying of liquids is more dependent on the presence of particulate matter and the nutrient content rather than general physical properties such as volume, osmolarity, viscosity and density.

The rate of gastric emptying was slower in female subjects than in males for all three drinks, although statistical significance was not reached due to the relatively small

sample size. These gender differences have been described previously and may be due to the effect of female sex hormones, especially progesterone, on gastric smooth muscle (Datz et al, 1987;Degen et al, 1996;Lobo et al, 2002). These differences were relatively small and it is uncertain whether gender related differences are clinically relevant.

MRI evaluation of gastric emptying has been validated against scintigraphic techniques (Feinle et al, 1999). The gastric emptying results for the CCD presented in this chapter are very similar to the results obtained with the same drink by Nygren et al (Nygren et al, 1995) using scintigraphy. However, the measurements made by the two techniques are, in fact, slightly different. Scintigraphy measures the residual isotope in the stomach and not the volume of the contents, while MRI measures the actual volume of the gastric contents, which is the sum of the volume of the drink administered and the volume of oro-gastric secretions. The gastric volume measured by MRI may, therefore, be increased by feeds that increase gastric secretion significantly. Amino acids stimulate gastrin release (Taylor et al, 1982) and, hence, gastric secretion (Kidd et al, 1998) and therefore may increase gastric volumes resulting in the appearance of a delayed gastric emptying rate.

The gastric residual volume had returned to the fasting baseline within 120 minutes of ingesting CCD, once again confirming that it is safe to administer such clear liquids up to two hours prior to the induction of anaesthesia. However, for ONS400 and ONS300 the mean residual gastric volumes at 120 min were still significantly greater than the baseline fasting levels, suggesting that a two-hour preoperative fast after ingesting these drinks may not be adequate. At 180 min the residual gastric volumes

had returned to baseline for both ONS400 and ONS300, suggesting that administration of these drinks three hours prior to induction of anaesthesia may be safe. We can, therefore, recommend that unless significant comorbidity is present, the period of preoperative fasting after ingestion of 300 – 400 ml of a liquid suspension should be between three and four hours.

Although the present data was from a study of healthy volunteers the results can be extrapolated to other groups. Preoperative anxiety in surgical patients has been shown to have no effect on gastric emptying time (Nygren et al, 1995) and morbidly obese patients have been shown to have similar gastric emptying patterns to lean patients (Maltby et al, 2004). Diabetic patients with autonomic neuropathy can, however, have delayed gastric emptying, increasing the risk of aspiration (Kong et al, 2005) therefore results obtained from healthy subjects may not be applicable to this group of patients. However, patients with uncomplicated type-2 diabetes can have gastric emptying times comparable with the subjects of the present study and a previous study on preoperative carbohydrate loading did not find an increased aspiration rate in type-2 diabetic patients (Breuer et al, 2006). Therefore it may be possible to extrapolate the results of this Chapter to otherwise health type-2 diabetic patents (Gustafsson et al, 2008).

The benefit of carbohydrate loading itself appears to be a result of an enhanced action of a 'postprandial' insulin surge at the start of surgery. The postprandial rise in glucose following such a carbohydrate load lasts for up to two hours in non-diabetic patients, which then enhances the action of insulin by approximately 50 % at three hours (Nygren et al, 1998). The additional delay between administration of the

carbohydrate load of the new drink and induction of anaesthesia and its slower gastric emptying profile is likely to alter the timing and the magnitude of this improved insulin response. Further studies will be required prior to recommendation of this novel product in place of a carbohydrate only preparation.

# SECTION F. INTERACTION OF NUTRITIONAL CONDITIONING AND LAXATION COMPONENTS OF THE ERAS PROTOCOL: A PROSPECTIVE RANDOMISED TRIAL

# *Chapter 8. Randomised clinical trial of laxatives and oral nutritional supplements within an enhanced recovery after surgery protocol following liver resection*

## 8.1 Background

Major abdominal surgery has a profound negative effect on patients' physiology and nutritional status. Left unchecked the metabolic response to injury can result in a prolonged recovery period, increased postoperative morbidity and longer length of hospital stay (Desborough, 2000;Nygren et al, 2005). The key components that are thought to delay postoperative recovery include postoperative pain, gastrointestinal dysfunction and immobility (Fearon et al, 2005). Enhanced Recovery After Surgery (ERAS) programmes combine a series of interventions to target these factors. Such protocols have been shown to be safe and effective, accelerate postoperative recovery and reduce length of hospital stay following aortic aneurysm repair (Podore et al, 1999), oesophagectomy (Cerfolio et al, 2004) and most notably colorectal resection (Basse et al, 2000). Within Chapter three of the present thesis the effectiveness of such a protocol is also demonstrated for patients undergoing hepatic resection.

Evidence for the efficacy of many of the individual protocol elements within an ERAS programme is often extrapolated from traditional care pathways (Fearon et al, 2005). The rate of morbidity and length of hospital stay following liver resection are relatively predictable. Thus, liver resection provides a suitable human model for testing the contribution of the individual elements within an ERAS programme in a randomised controlled trial (Belghiti et al, 2000).

Reduced gastrointestinal function after surgery is a major factor that limits the overall success of an enhanced recovery programme. Current enhanced recovery protocols employ a multi-modal package with elements that include; continuous thoracic epidural anaesthesia, enforced mobilisation and avoidance of excessive saline load. All of which, in the context of traditional perioperative care, have been shown individually to reduce postoperative ileus (Lobo et al, 2002;Fotiadis et al, 2004;Nisanevich et al, 2005). In addition to these factors, early feeding after open elective abdominal surgery is associated with earlier passage of flatus and stool (Stewart et al, 1998). Despite the widespread use of laxatives in non-surgical patients there are limited data regarding their routine use in the postoperative period. The administration of magnesium hydroxide, a known osmotic purgative, has been described in an unblinded, non-randomised study and has been employed in ERAS programmes, however, there is limited evidence to justify routine use (Fanning et al, 1999;Basse et al, 2000;Hansen et al, 2007). It has also been suggested that preoperative carbohydrate loading may promote earlier return of gastrointestinal function (Noblett et al, 2006). Within an ERAS protocol, metabolic conditioning and early provision of oral nutritional supplements may interact with laxatives to enhance gastrointestinal function further in the early postoperative phase.

Early recovery of gastrointestinal function allows early oral intake, discontinuation of intravenous fluids and hence accelerated recovery. Early food intake may attenuate postoperative catabolism. Preoperative oral carbohydrate loading has also been shown to reduce the postoperative catabolic response and insulin resistance (Nygren et al, 1998;Soop et al, 2001). By improving the ability of a patient to respond to anabolic

stimuli in the postoperative period, metabolic preconditioning may promote greater benefit from early postoperative nutritional intake. The perioperative administration of oral nutritional supplements (ONS) has been shown to improve nutritional status and reduce minor complications within the context of traditional perioperative care (Beattie et al, 2000;Smedley et al, 2004). It is not known if the provision of combined metabolic conditioning / early oral nutritional support along with early recovery of gastrointestinal function achieved with magnesium hydroxide, can promote further improvements in the rate of overall functional recovery within an ERAS protocol.

The aim of the Optimised Recovery Accelerated Nutrition and Gastrointestinal Enhancement (ORANGE) study presented in this chapter was to determine, within an ERAS protocol designed for hepatic resection, whether postoperative bowel stimulation with magnesium hydroxide and / or metabolic conditioning / oral nutritional supplements are effective in promoting early return of gastrointestinal function and overall postoperative recovery.

## 8.2 Patients and methods

The results presented in this chapter were obtained as part of a prospective randomised controlled trial with a two-by-two factorial design assessing the effect of routine postoperative laxation and its interaction with early administration of oral nutritional supplements for patients undergoing hepatic resection within an ERAS care protocol. This trial was conducted with the approval of Lothian Research Ethics committee. All recruited patients were programmed to undergo hepatic resection for benign or malignant conditions at the Liver Unit at Edinburgh Royal Infirmary Edinburgh, UK or Maastricht University Medical Centre, The Netherlands, between July 2006 and June 2008. All were aged between 18 - 80 years of age, had a BMI of between 18 and 30 $Kg / m^2$ and had no pre-existing limitations to mobility or underlying cirrhotic liver disease. Informed, written consent was obtained from all patients recruited.

Suitable patients were recruited during an outpatient pre-assessment visit at least one week prior to hospital admission allowing a suitable time for reflection prior to providing written, informed consent. Patients received preoperative information packs and counselling related to the perioperative ERAS care pathway. They were informed about the protocol and the importance of both early mobilisation and early oral intake. Following recruitment and prior to hospital admission patients were randomised to one of four groups (Control, Laxation, ONS and Laxation & ONS) using consecutively sealed, opaque envelopes created in advance through block randomisation with a random numbers table. Patients randomised to the laxation group received 1g of Magnesium hydroxide orally twice daily from the day of surgery

until the day of discharge. Patients randomised to ONS group received 800 ml of a carbohydrate loading drink (Nutricia Preop® Nutricia Clinical Care, Trowbridge, UK.) at 10 pm the night before surgery and 400 ml at 6 am on the morning of surgery. In addition, they received ONS (two cartons per day comprising 400 ml, 600 kcal, 24 g protein, Nutricia Fortisip®; Nutricia Clinical Care). Patients randomised to the laxation & ONS received the combined elements of the laxation group and the ONS group. Owing to the nature of the study interventions (nutritional supplements available in a variety of flavours to encourage compliance and magnesium hydroxide suspension produced by the hospital pharmacy), a suitable placebo was not feasible and so the type of treatment could not be masked. All patients followed a standardised perioperative and anaesthetic regimen based on previously published ERAS protocol (Fearon et al, 2005). The study groups are summarised in Table 8.1.

**Table 8.1: Summary of four different group protocol following randomisation within 2 x 2 factorial study**

| | |
|---|---|
| **Control** | **Laxation**<br><br>1 gram of magnesium hydroxide twice daily from day of surgery until discharge from hospital |
| **ONS**<br><br><u>Preop</u><br>800 ml of oral carbohydrate-loading drink at 10 pm the night before surgery and 400 ml at 6 am on the morning of surgery<br><br><u>Postop</u><br>Two cartons of oral nutritional supplement per day from day of surgery until day 30 | **Laxation & ONS** |

A standardised perioperative and anaesthetic regimen based on a published colorectal ERAS protocol, was followed (Fearon et al, 2005). This multi-modal, enhanced recovery programme described in Chapter 3 of the present thesis was modified to cover all aspects of liver resection. Notably, liver tissue sealant (TachoSil®, Nycomed, Zurich, Switzerland) was used to minimise bile leakage and haematoma formation, routine perihepatic drainage was avoided and paracetamol used at the discretion of the surgeon in cases of extended resection. Patients were normally scheduled for surgery in the morning and were nursed in a high dependency unit. Details of the ERAS liver protocol are shown in Table 8.2.

**Table 8.2: Care plan for patients undergoing liver resection within ERAS Protocol**

| | |
|---|---|
| **Day before surgery** | Normal feeding until midnight<br>No preanaesthetic medication |
| **Day of Surgery** | Mid-thoracic epidural analgesia (local anaesthetic and low-dose opioid)<br>Short acting anaesthetic agent<br>No naso-gastric tube (if used removed immediately after surgery)<br>Warm IV fluids and body warming device<br>Avoidance of excessive IV fluids<br>No routine drainage of peritoneal cavity<br>Oral intake of water/nutrition started immediately ad libatum<br>Patients out of bed for 2 hours |
| **Postoperative day 1** | Patient mobilised<br>IV fluids discontinued<br>Patient to drink at least 1 litre of fluid<br>Normal diet<br>Continue mid-thoracic epidural analgesia<br>1 g of Paracetamol QDS |
| **Postoperative day 2** | Continue mid-thoracic epidural analgesia<br>1 g of Paracetamol QDS<br>Normal diet<br>Patient mobilised |
| **Postoperative day 3** | Stop epidural<br>Commence NSAIDs if appropriate<br>Remove urinary catheter<br>Encourage full oral intake and mobilisation<br>Review discharge criteria |
| **Postoperative day 4** | Encourage full oral intake and mobilisation<br>Review discharge criteria |

The above table is based on Table 3.1 in the present thesis, however, preoperative carbohydrate loading, postoperative oral nutritional supplements and postoperative magnesium hydroxide were administered according to randomisation.

Seven specialist liver surgeons performed all resections between the two centres. Extent of resection was classified according to Brisbane 2000 Terminology (International Hepato-Pacreato-Biiary Association, 2000). Subcostal incisions were used and the transection plane determined by preoperative imaging and using intraoperative ultrasonography. Resection was performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA®; Valleylab, Boulder, Colorado, USA) and argon beam coagulation. After removal of the liver specimen, the raw surface of the liver remnant was subjected to Argon beam coagulation and sealed with TachoSil®. Abdominal drains were not placed routinely and the abdomen was closed with a standard running suture.

Study data were documented prospectively during the hospital stay and 30 days after surgery at an outpatient visit. Return of gastrointestinal function was determined by first passage of stool post surgery. Patients were assessed for return of GI function (passage of flatus/stools) on a daily basis. Secondary outcomes were: postoperative oral nutritional intake on postoperative days 1 – 3, functional recovery and length of hospital stay.

**Oral nutritional intake**

A senior dietician, in cooperation with the patient and ward nursing staff, recorded postoperative oral intake daily for all patients on a standard diet sheet. This was converted to energy intake (in kilocalories) intake and the recommended nutritional intake (RNI) for each subject was estimated using CompEat Pro® for Windows® (Nutrition Systems, Banbury, England). The percentage RNI achieved on

postoperative days 1 - 3 for each of the subjects was used in comparisons between the study groups.

**Functional recovery criteria**

Functional recovery was defined as in Chapter 3. Adequate pain control requiring only oral analgesia, adequate oral intake with no IV fluid requirement, independent mobility sufficient to perform activities of daily living and blood results (liver function tests and inflammatory markers) returning towards normal ranges. Criteria were assessed on a daily basis. An experienced clinician determined readiness for hospital discharge. Time to achieve functional recovery, initial length of stay (defined as the number of nights spent in hospital after surgery, excluding readmissions) and all adverse events up to 30 days were recorded. Morbidity was documented prospectively according to criteria described previously (Copeland et al, 1991;Lang et al, 2001). Other data recorded for each patient included mortality, readmissions and use of preoperative chemotherapy.

**Statistical analysis**

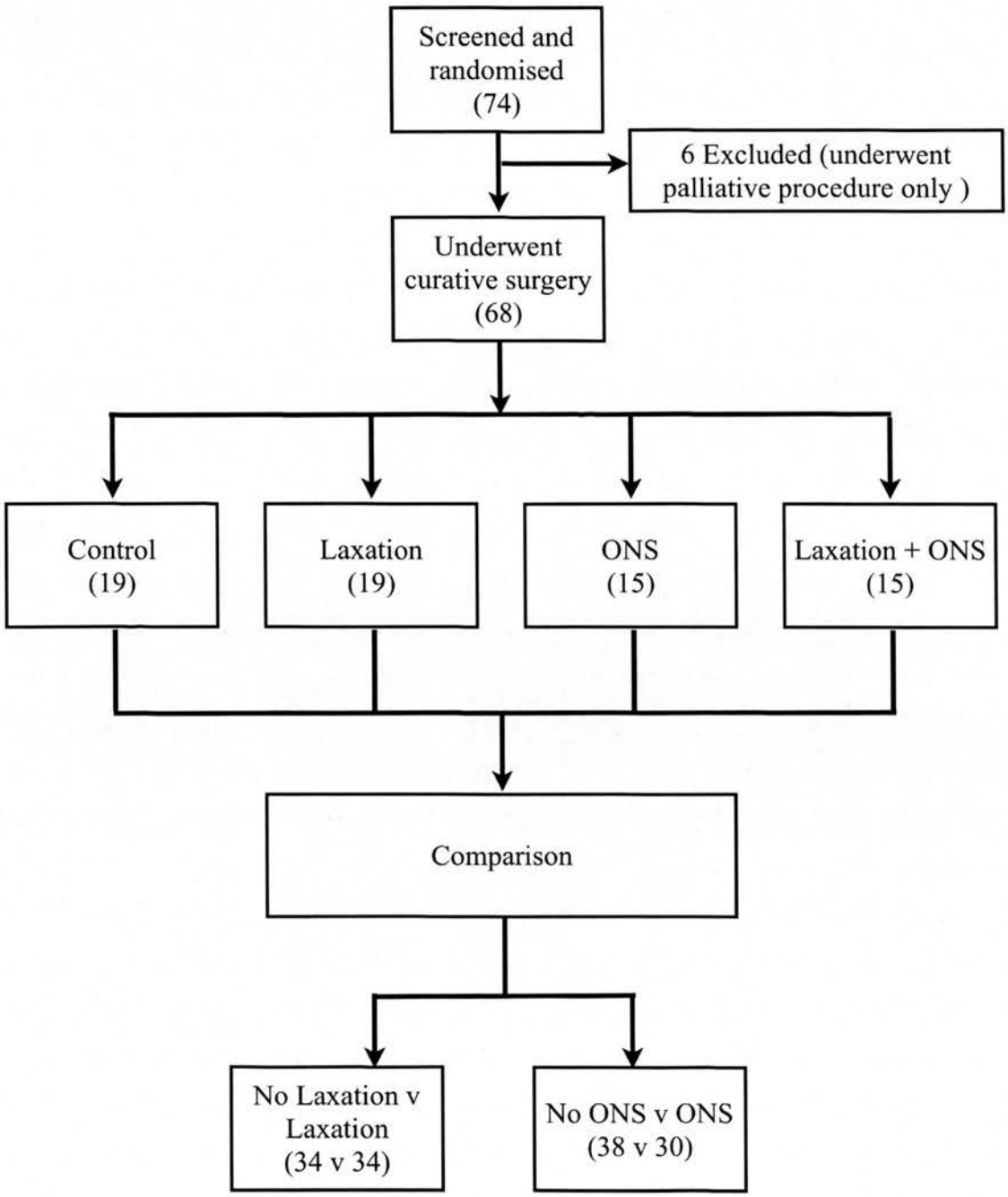
Retrospective data (P.O. Hendry and K.C.H. Fearon, unpublished results) indicated that the mean (s.d) time to passage of stool was 5.3 days +/- 1.3 days. This study was powered ($\alpha = 0.05$, $\beta = 0.80$) on the primary outcome to detect a 20 % difference in time to passage of stool, the primary outcome. Based on this calculation, fourteen patients were required in each of the four groups (56 patients overall). The secondary endpoints were of an exploratory nature. Continuous data are expressed as median (IQR) and categorical variables as incidence (percentage). For comparison between the study groups, data were analysed using Mann-Whitney test, chi-squared

test or Fisher's exact test where appropriate. $P < 0.05$ was considered statistically significant. SPSS® version 17.0 for Mac® (SPSS, Chicago, Illinois, USA) was used for data analysis.

## 8.3 Results

Between July 2006 and June 2008, 74 patients were recruited and randomised within the ORANGE study, sixty-six in Edinburgh and eight in Maastricht. Six patients did not undergo hepatic resection and were excluded. The remaining 68 patients were managed within the ORANGE protocol as outlined previously (Fig 8.1).

**Fig 8.1: Consort diagram for patients undergoing liver resection within an ERAS protocol and randomised in a 2 x 2 factorial design to Control, Laxation, ONS and Laxation or ONS.**



Demographics for the four study groups are shown in Table 8.3. Overall the male to female ratio was 4:3 and the median (IQR) age was 62 (53,69) years. Sixty-two patients (91 %) were treated for malignant disease. There were no significant differences across the study groups for sex, American Society of Anesthesiologists (ASA) Grade, pathology, malignancy, body mass index, use of neoadjuvant therapy or extent of liver resection (Table 8.3). There were 53 major and 15 minor resections (Table 8.4).

**Table 8.3: Demographics of 68 Patient undergoing liver resection within an ERAS protocol of care and randomised in a 2 x 2 factorial design to Control, Laxation, ONS and Laxation or ONS.**

| | **Overall** 68 | **No Laxation** 34 | **Laxation** 34 | **p** | | **No ONS** 38 | **ONS** 30 | **p** |
|---|---|---|---|---|---|---|---|---|
| Age (years)* | 62 (53,69) | 62 (51,70) | 61.5 (55,69) | 0.722† | | 64.59 (51,70) | 61 (52,63) | 0.243† |
| M:F | 38:30 | 21:13 | 17:17 | 0.464‡ | | 20:18 | 18:12 | 0.626‡ |
| ASA | | | | | | | | |
| 1 | 15 (22.1) | 7 (20.6) | 8 (23.5) | | | 9 (23.7) | 6 (20.0) | |
| 2 | 43 (63.2) | 20 (58.8) | 23 (67.6) | | | 23 (60.5) | 20 (66.7) | |
| 3 | 10 (14.7) | 7 (20.6) | 3 (8.8) | 0.391‡ | | 6 (15.8) | 4 (13.3) | 0.973‡ |
| 4 | 0 (0.0) | 0 (0) | 0 (0) | | | 0 (0) | 0 (0) | |
| BMI* | 22 (22.5,28) | 25.25 (22.6,30.5) | 24.95 (22.3,28) | 0.394† | | 25.05 (22.2,28.0) | 25.1 (22.6,28.9) | 0.882† |
| Pathology | | | | | | | | |
| Malignant Disease (n) | 62 (91.2) | 30 (88.2) | 32 (94.1) | 1‡ | | 35 (92.1) | 27 (90.0) | 1‡ |
| Colorectal Liver Metastases | 56 (82.4) | 26 (76.5) | 30 (88.2) | | | 31 (81.6) | 25 (83.3) | |
| Other metastatic disease | 6 (8.8) | 4 (11.8) | 2 (5.9) | | | 4 (10.5) | 2 (6.7) | |
| Benign disease | 6 (8.8) | 4 (11.8) | 2 (5.9) | 0.445‡ | | 3 (7.9) | 3 (10.0) | 0.829‡ |
| Neoadjuvant therapy (n) | 22 (32.4) | 9 (26.5) | 13 (38.2) | 0.127‡ | | 13 (34.2) | 9 (30.0) | 0.797‡ |

Values in parentheses are percentages unless indicated otherwise; *values are median (interquartile range). † Mann-Whitney U Test ; ‡ $\chi^2$test. ASA = American Society of Anesthiologists Grade, BMI = Body Mass Index.

**Table 8.4: Extent of Liver Resection for sixty-eight patients following an ERAS protocol of care randomised in a 2 x 2 factorial design to Control, Laxation, ONS and Laxation or ONS.**

| Operation | Overall n=68 | No Laxation 34 | Laxation 34 | p | | No ONS 38 | ONS 30 | p |
|---|---|---|---|---|---|---|---|---|
| Major (trisectionectomy, central hepatectomy, hemihepatectomy) | 53 | 25 (73.5) | 28 (82.4) | | | 31 (81.6) | 22 (73.3) | |
| Minor (sectionectomy, segmentectomy, metastasectomy) | 15 | 9 (26.5) | 6 (17.6) | 0.560§ | | 7 (18.4) | 8 (26.7) | 0.557§ |

Values in parentheses are percentages. § Fisher's exact test.

Time to functional recovery and initial length of hospital stay [median (IQR)] were 4 days (3,5) and 6 days (4,7) respectively and were not significantly different between the study groups. The postoperative morbidity was 25%, and did not differ significantly between the groups (Table 8.5). Two patients required reoperation due to postoperative haemorrhage. Five patients required readmission to hospital (intra-abdominal collection, 2; severe constipation, 1; bile leak, 1; pneumonia, 1). There were two deaths due to myocardial infarction within 30 days of surgery. Discharge from hospital was delayed in some patients for reasons outlined in Table 8.6.

**Table 8.5: Primary Outcome Data for sixty-eight patients undergoing liver resection within an ERAS protocol of care and randomised in a 2 x 2 factorial design to Control, Laxation, ONS and Laxation or ONS.**

| | Overall n=68 | No Laxation 34 | Laxation 34 | p | | No ONS 38 | ONS 30 | p |
|---|---|---|---|---|---|---|---|---|
| **Time to first drink** | 0 (0,0) | 0 (0,0) | 0 (0,0) | 1.000† | | 0 (0,0) | 0 (0,0) | 0.808† |
| **Time to first food** | 1 (1,1) | 1 (0,1) | 1 (0,1) | 0.218† | | 1 (0,1) | 1 (0,1) | 0.499† |
| **Time to first flatus** | 3 (2,4) | 3 (2,4) | 2.5 (2,3.5) | 0.108† | | 3 (2,5) | 3 (2,4) | 0.262† |
| **Time to first stool** | 5 (4,6) | 5 (4,6) | 4 (3,5) | 0.034† | | 5 (4,7) | 4 (3,5) | 0.076† |
| **Time to functional recovery** | 4 (3,5) | 4 (3,4.5) | 4 (3,5) | 0.242† | | 4 (3,5) | 4 (3,4) | 0.110† |
| **Initial hospital stay** | 6 (4,7) | 5 (4,6) | 6 (5,8) | 0.081† | | 6 (5,7) | 5 (4,7) | 0.367† |
| **Readmission*** | 5 (7.4) | 3 (8.82) | 2 (5.9) | 1.000§ | | 3 (7.9) | 2 (6.7) | 1.000§ |
| **Reoperation*** | 2 (2.9) | 1 (2.9) | 1 (2.9) | 1.000§ | | 2 (5.3) | 0 (0.0) | 0.504§ |
| **30-day morbidity*** | 17 (25) | 8 (23.5) | 9 (26.5) | 1.000§ | | 11 (28.9) | 6 (20.0) | 0.574§ |
| **30-day mortality*** | 2 (2.9) | 2 (5.9) | 0 (0.0) | 0.494§ | | 2 (5.3) | 0 (0.0) | 0.500§ |

Values are median (interquartile range) unless indicated otherwise; *Values in parentheses are percentages.
† Mann-Whitney U Test test; §Fisher's exact test.

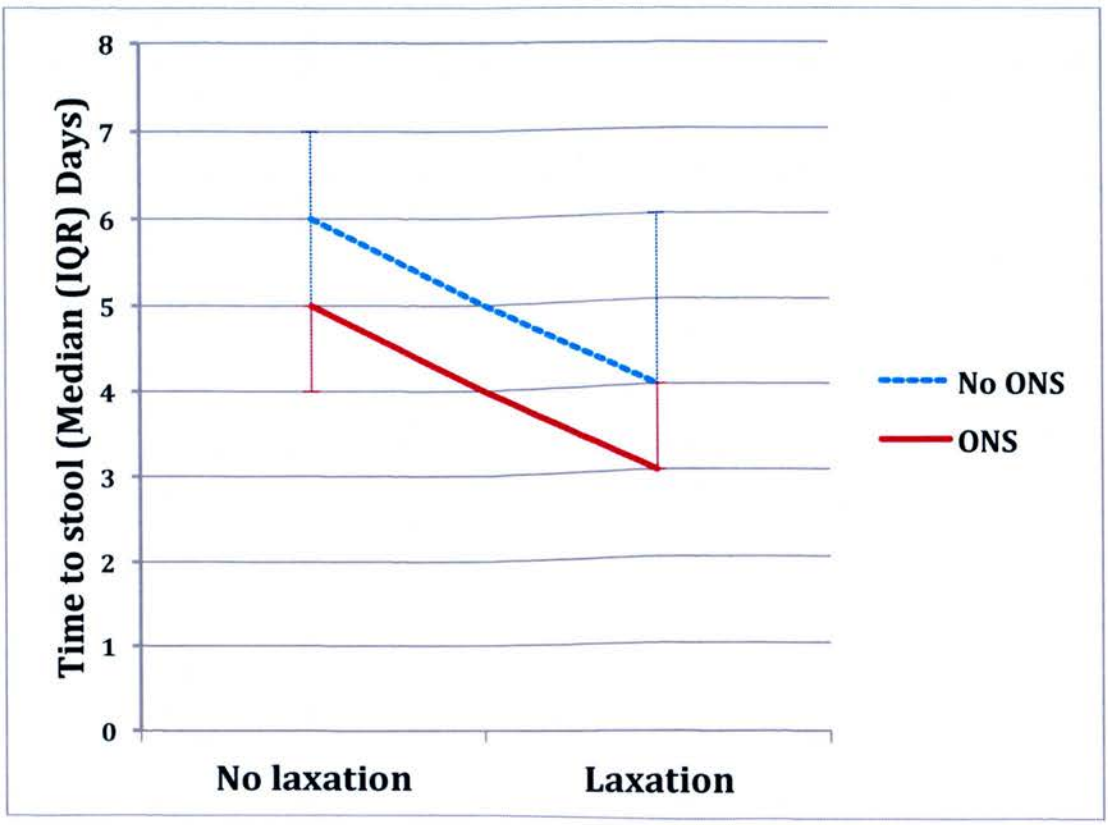
**Table 8.6: Reasons for hospital stay beyond achievement of functional recovery criteria**

| Reason | No of patients |
|---|---|
| Caution over discharge due to earlier complication or extensive surgery | 5 |
| Patient did not feel confident to be discharged | 4 |
| Transport/social problems | 2 |
| Patient boarded to another ward prior to discharge | 1 |
| Patient drowsy due to analgesia administered | 1 |

Oral fluid intake was resumed on the day of surgery in 94 % of patients. Reintroduction of diet was achieved on day one in 37 % of patients and day two in 91 %. Intravenous fluids were discontinued on postoperative day one in 51 % of patients and by day two in 78 %. Mid-thoracic epidural anaesthesia was commenced before surgery in 99 % of patients and continued for at least 48 hours post-surgery in 93 % of patients, 4 epidurals failed on day one. Drains were used in nine patients (13 %). Nineteen patients (28 %) achieved mobilisation on the day of surgery. Sixteen patients (24 %) had a urinary catheter in situ beyond discontinuation of epidural analgesia and 32 (47 %) of patients received non-protocol IV fluids in the perioperative period.

Overall, the median (IQR) time to passage of stool was 5 (4,6) days. Patients randomised to ONS showed a trend to shorter time to passage of stool (4 (3,5) vs 5 (4,7) days: p=0.076). Patients randomised to laxation had a significantly reduced time to passage of stool (4 (3,5) vs 5 (4,6) days: p=0.034). Patients randomised to the combination regimen also had a significantly reduced time to passage of stool (3 (3,4) vs 6 (4,7) days: p = 0.013). There was no evidence of interaction between laxatives and ONS (Fig 8.2).

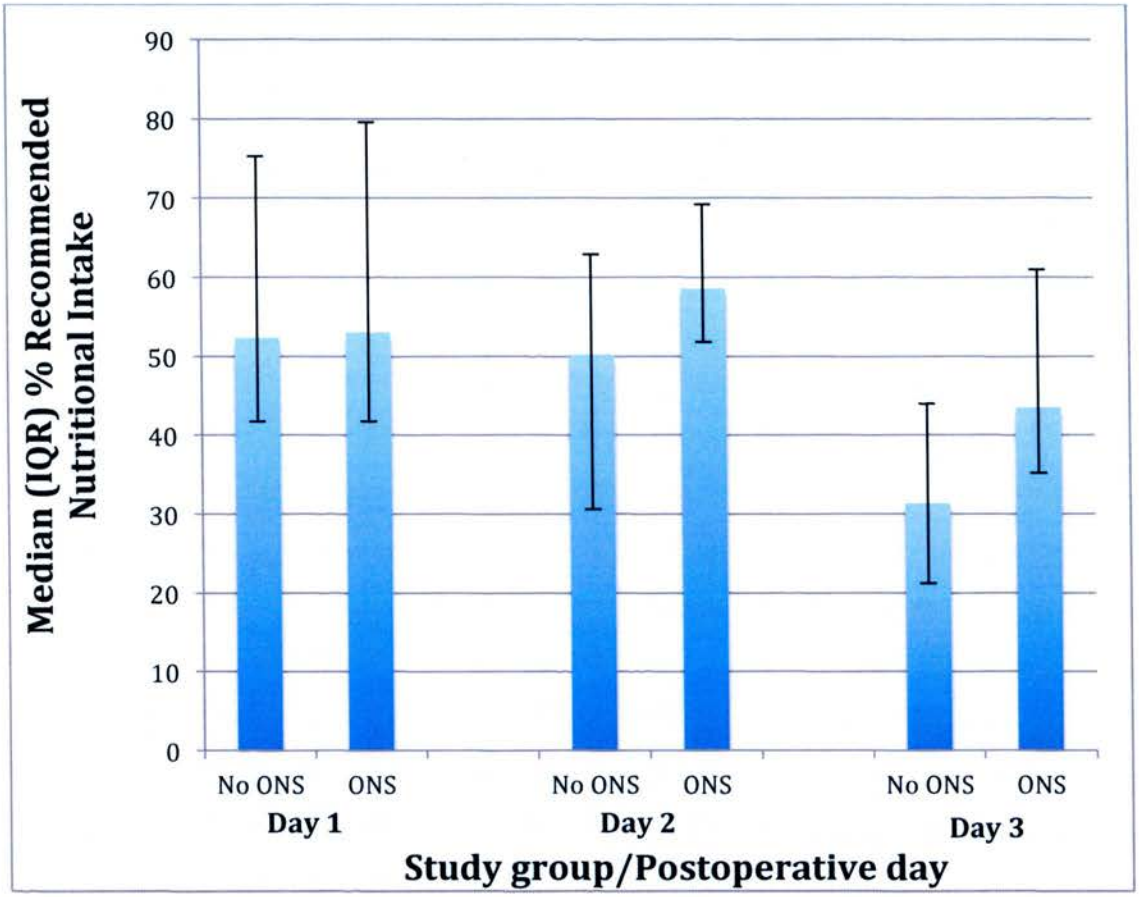
**Fig 8.2: Diagram of potential interaction between laxatives and oral nutritional supplements (ONS) in sixty-eight patients undergoing liver resection within an ERAS protocol of care randomised in a 2 x 2 factorial design to Control, Laxation, ONS and Laxation or ONS.**




Values are median with interquartile range.

Oral intake of at least fifty percent of recommended nutritional requirement was achieved at a median (IQR) of 1 (1,2) days after surgery for the whole group. This was not significantly different between groups. Total calorie intake (including ONS) on postoperative days 1 - 3 for those randomised to the ONS was not significantly different from that in patients who did not receive ONS (Fig 8.3). The median (IQR) percentage change in body weight from preoperative level for all subjects was +1.8% (-1.4,5.8) and -2.0% (-4.7, -0.3) on postoperative day five and day thirty respectively and there were no significant differences between the groups ($p = 0.166$ and 0.200 respectively).

**Fig 8.3: Total calorie intake during the first 3 days after liver resection for sixty-eight patients following an ERAS protocol of care receiving ONS supplements or no ONS supplements.**




Values are median with interquartile range. ONS = oral nutritional supplements

## 8.4 Discussion

Within the study presented in this chapter, laxatives significantly decreased the time to passage of stool after liver surgery. Patients randomised to the combination regimen also had a significantly reduced time to passage of stool but with no evidence of interaction between laxation and ONS. There were no differences in the secondary outcomes between groups.

Previous studies have suggested that early restoration of food intake can result in a more rapid return of gut function in the postoperative period (Stewart et al, 1998). In the present study, the total calorie intake (food plus ONS) of the groups randomised to ONS was not significantly different from patients who did not receive ONS, suggesting that ONS in the early postoperative phase suppressed normal food intake to the point at which there was no net benefit. The lack of interaction between laxation and ONS could therefore be explained on the basis that ONS did not alter overall calorie intake and may also explain the lack of effect of ONS on the secondary outcomes.

Patients following the ERAS protocol recommenced oral fluid intake on the day of surgery, started eating the day after surgery, were mobile by the third postoperative day and achieved discharge criteria on the fourth postoperative day. Median length of hospital stay was 6 days, which is significantly shorter than the 8-14 days reported in other centres following a more traditional pattern of perioperative care (Jarnagin et al, 2002;Dimick et al, 2004;Capussotti et al, 2006;Petrowsky et al, 2006). The results in this chapter are in keeping with those in Chapter 3 and provide further evidence to support the use of an ERAS pathway following liver resection to accelerate

postoperative recovery and shorten length of hospital stay. In the present study, functional recovery was achieved a median of four days following surgery, a median of two days before actual discharge from hospital. It may be possible to achieve a shorter overall hospital stay by further tightening the care pathway elements of the protocol (Maessen et al, 2007).

In this study, the overall morbidity rate was 25 %, readmission rate 7.4 % and mortality rate 2.9 %. Morbidity rates in the present study were lower and mortality rates in keeping with those published from other countries following traditional care pathways (38 – 45 % and 2.7 – 3.1 % respectively) (Jarnagin et al, 2002;Petrowsky et al, 2006;Nikfarjam et al, 2009).

All patients received preoperative counselling and there was a high level of compliance with most elements of the protocol. Ninety-nine percent of patients received preoperative epidural anaesthesia. Intraoperative drainage was only used in cases considered to have a higher risk of a bile leak (13 %), in keeping with current evidence (Fong et al, 1996;Burt et al, 2002).

In the early postoperative period, adherence to the protocol was lower than that observed in the preoperative and intraoperative phases. This is in keeping with the earlier findings in the present thesis and supported by other published data (Maessen et al, 2007). Intravenous fluids were discontinued on the day after surgery in only half of the patients. Saline (0.9 %) was prescribed by out-of-hours medical staff, less familiar with the study protocol, 47 % of patients received at least 200 ml of IV saline. Only 28 % of patients were mobilised on the day of surgery. This was usually

due to epidural-related hypotension or late return to the high dependency unit. Future ERAS protocols may overcome the issue of late return to the ward by initiating postoperative mobilisation in the recovery room. Postoperative variables are both markers of protocol compliance and markers of recovery and therefore patients achieving these protocol goals are those likely to achieve a faster overall recovery.

Within the context of multimodal therapy it is difficult to separate the effect of one protocol component from another. A two-by-two factorial design is an efficient way of assessing two different factors and evaluating their potential interaction. The statistical design of the study presented in this chapter meant that there was a potential confounder in 50 per cent of each group under description; this reflects the exploratory nature of the evaluation of potential interactions.

The present study has shown that laxatives can hasten return of colonic function in patients undergoing hepatic resection. However, there was no evident interaction with ONS. More importantly, there seemed to be no benefit in terms of enhanced oral intake or overall functional recovery. Thus the benefit for the patient of routine laxatives or ONS is difficult to gauge. Clearly the present findings cannot be extrapolated directly to patients with an intestinal anastomosis. Future studies might also evaluate the interaction between the present variables and other measures designed to improve upper gastrointestinal function and oral intake.

# SECTION G. GENERAL DISCUSSION

## *Chapter 9. Conclusions*

### 9.1 Enhanced Recovery After Surgery

It is important that perioperative care continues to evolve and incorporate an evidence base to its practice. Despite the widespread discussion of enhanced recovery after surgery protocols, ward level practice is often based on outdated aphorisms. Even within ERAS programmes themselves much of the evidence for the individual elements is taken in isolation from traditional care pathways, consensus review or simply accepted standards of care [as described in Chapter 1.3,1.4]. Little evidence is available concerning the importance of each element when considered within the context of an enhanced recovery pathway. There is extensive literature in the area of Enhanced Recovery After Surgery, however, only a limited number of randomised controlled trials have been reported (Spanjersberg et al, 2011). Further refinement of the ERAS protocol will rely on evaluation of the individual protocol elements within randomised controlled trials, improved protocol compliance and audit of objective postoperative outcomes. Length of hospital stay itself has been questioned as an appropriate measure of protocol success (Maessen et al, 2008). Outcomes such as gastric emptying rate or activity level may represent feasible, objective markers of recovery (Chapters 4 and 5) along with more accurate measures of postoperative morbidity and will allow individual or combinations of components of the ERAS protocol to be tested within clinical trials.

## 9.2 The application of an ERAS care pathway to high-risk patients.

Modern surgical care has to account for an aging population with increasingly complex comorbidity and undernutrition. The multimodal ERAS protocol of care represents a potential solution. Chapter 2 of this thesis presents a mixed group of over one thousand patients undergoing colorectal resection within such a programme. In this group almost one in five were over eighty years old, one in five had an ASA of 3 or more and one in twelve a BMI of under 20 kg / $m^2$. Despite this, hospital stay was 6 days, overall morbidity was 28.4 % and mortality 1.6 %. Morbidity was significantly lower than that predicted by the P-POSSUM system and both morbidity and mortality were lower than rates published by other European centres following traditional perioperative care pathways (Braga et al, 2002;Alves et al, 2005). Length of stay was also shorter than that published for open (Nygren et al, 2005) or laparoscopic techniques (Guillou et al, 2005;Veldkamp et al, 2005) following traditional care. This attests to the general safety and potential benefits of the ERAS approach to perioperative care.

The same study demonstrated that neither BMI below 20 kg/$m^2$ nor age 80 years or more were independent predictors of postoperative 30-day morbidity or mortality. This is in contrast with traditional perioperative care (Polanczyk et al, 2001) and mortality (Alley, 2000;Tekkis et al, 2003). Mortality rate for those aged 80 years or above (3.1 %) [Chapter 2], compared favourably with published figures (1.1 - 11.3 %) (Heriot et al, 2006;Ong et al, 2008). Therefore, within the context of an enhanced recovery programme the surgeon may not need to individualise postoperative morbidity or mortality risk assessment for elderly or undernourished

patients as relatively stress-free surgery and minimisation of organ dysfunction appear to translate into reduced morbidity and the apparent attenuation of the increased surgery risk.

Postoperative complications in the elderly have been shown to be independent predictors of decreased long-term survival (Manku et al, 2003) therefore, improvement in 30 day morbidity is of increased significance in this group of patients. If older patients make it through the immediate postoperative period 5-year survival in those aged 80 years or more is similar to that of the younger group (Smith et al, 2002). The favourable outcomes reported for patients over 80 years old, in the present thesis may reflect some degree of selection bias. However, this seems unlikely given that the patient series was consecutive. In this thesis, age was related to time to mobilisation and length of hospital stay. In this age group a prolonged length of hospital stay itself may also reflect difficulties in arranging social care post discharge (Maessen et al, 2007;Maessen et al, 2008).

Comorbidity is still a significant factor in predicting postoperative outcomes in both traditional care and enhanced recovery pathways. However, the present study demonstrates lower rates of morbidity within an ERAS protocol despite one in five patients having significant comorbidity (ASA 3 or more), which suggests that this comorbidity is modulated by the ERAS approach.

Within Chapter 2 it is demonstrated that the ERAS protocol represents an overall strategy to condition all patients and to improve all aspects of perioperative care. This should be easier to implement than the provision of specialised care for a difficult-to-

define group of individual patients. The improved postoperative outcomes achieved with the ERAS protocol would appear to be an improved rate of morbidity in potentially high risk patients alongside reduced recovery period and length of hospital stay in patients with lower perioperative risk profiles.

There are limitations to the results in this chapter. Although the results of this chapter were gathered from a large, multicentre, prospective database of over a thousand consecutive, unselected patient, the original aim of the database was to audit improvement in length of hospital stay as each unit introduced an ERAS programme and became more familiar with its day-to-day application. The initial database did not aim to differentiate between the postoperative outcomes of higher risk groups of patients: elderly, malnourished and those with major comorbidity.

Perioperative Nutrition is an important factor in the ERAS protocol and within the existing database BMI was recorded as a measure of nutritional status. BMI is a useful measure of nutritional status as it is universal, easily understood and does not require measurements outwith those normally recorded at hospital admission. It can, however, be flawed notably in overweight patients with unplanned significant weight loss and athletic patients who despite a low BMI will be physiologically optimal. Similarly although ASA is a robust and universally measure of categorising higher and lower risk patients it is more likely that risk is overestimated. There are more detailed and more objective scoring systems such as APACHE II that may provide more detailed evaluation of patients' comorbidity and surgical risk.

Further evaluation of the specific benefit of an ERAS programme of care for higher risk patient groups will require both a larger cohort of patients (ideally from a greater number of centres) and more detailed identification of the higher risk patients. Although the evaluation of age will not change, with the overall increase in average patient age our definition of elderly may rise. Moreover, in these groups a reduced length of hospital stay is less important as the most significant risks is from postoperative morbidity. Specific attention to postoperative complications is more desirable in these groups as this is often linked to longer-term survival. With complications such as surgical site infections and anastomotic leaks there is also a risk that early discharge pushes the diagnosis and initial management of such complications onto the primary care physician. It is particularly significant in this group to ensure that patients are beyond the high-risk period of such events prior to discharge. Although complications outwith the hospital environment can never be excluded discharge criteria should take into consideration potential early warning signs such as elevated CRP on postoperative day four (Warschkow et al, 2011). This would limit discharge to a minimum of four days after surgery.

The Malnutrition Universal Screening Tool (MUST) (BAPEN, 2003), could be used to assess nutritional status in more detail. This screening tool has already been shown to be user friendly and can identify undernourished and over nourished patients. Detailed food diaries could be used to compare preoperative and postoperative oral intake. Anthropometry (Percentage body fat, Lean body mass, mid arm muscle circumference and Triceps skinfold thickness) could provide much more detailed evaluation of nutritional status. Although anthropometry will require more time and specialist training it is likely to be the most useful measure of nutritional status before

and after surgery. Similarly for patient comorbidity from objective scoring systems such as P-POSSUM or APACHE II may allow a more objective assessment of the benefits of ERAS programmes for patients with significant comorbidity.

## 9.3 Hepatic resection as a model for enhanced recovery trials.

It is apparent that randomised controlled trials are necessary to further refine the ERAS protocol. Due to its predictable outcomes hepatic surgery is a suitable model in which to run such trials. In Chapter 3 the benefits of an Enhanced Recovery After Surgery programme are demonstrated in patients undergoing hepatic resection. Patients managed within the ERAS protocol were discharged from hospital a median of 6 days after surgery with half the cohort discharged within 5 days. This is considerably shorter than the length of stay reported by other European centres for traditional perioperative care (Jarnagin et al, 2002;Dimick et al, 2004;Capussotti et al, 2006). Adverse outcomes following liver resection (hospital readmissions, postoperative complications and deaths) were similar to the control group and complication rates in keeping with those published for traditional care (Jarnagin et al, 2002;Petrowsky et al, 2006;Schroeder et al, 2006;Benzoni et al, 2007;Figueras et al, 2007). Although, compared with the control group, the morbidity rate was higher in the ERAS group, the study was not sufficiently powered to determine statistical differences in the incidence of complications.

Preoperative elements of the ERAS protocol were readily accepted and implemented especially carbohydrate loading prior to surgery (Nygren et al, 1995;Brady et al, 2003). This was a dramatic improvement on the nil by mouth from midnight policy practiced in many surgical units. This trend towards ready adoption of new elements of the ERAS protocol is highlighted again in Chapter 6 where a complicated regimen of preoperative metabolic conditioning in combination with mechanical bowel preparation was applied. The present thesis, however, also highlights how slow some elements of perioperative care are to evolve. Despite evidence that in traditional

perioperative care nasogastric tubes are unnecessary and can result in more pulmonary complications (Cheatham et al, 1995;Nelson et al, 2007;Pessaux et al, 2007) they were still commonly used during surgery in the traditional perioperative care cohort from Maastricht [Chapter 3]. With the introduction of the ERAS protocol they were removed immediately after surgery, which was an improvement in clinical routine.

In the present thesis [Chapter 3] oral intake of water was tolerated within four hours of surgery and oral diet recommenced on the day after surgery in the ERAS group. Delayed return of gastrointestinal function (>7 days) occurred in 3 (5 %) of patients, which was not significantly different from the control group. However, the sample size was small and it is likely that complications such as this would be more closely assessed in the prospective ERAS group and may have been underestimated in the retrospective control group. Mobilisation on the day of surgery was possible in Edinburgh however, proved more difficult in Maastricht as the recovery unit did not contain the appropriate facilities or nursing staff required. Early oral intake, restrictive fluid IV therapy and early mobilisation are significant factors in the reduction of postoperative gastrointestinal dysfunction (Lewis et al, 2001;Kehlet et al, 2002;Lobo et al, 2002). Reduction in postoperative gastrointestinal dysfunction is likely to be a key factor in improving rate of functional recovery; therefore adherence to these elements is significant.

Chapter 3 demonstrates that patients with otherwise normal liver function can undergo curative resection of primary or secondary liver tumours within a multimodal enhanced recovery programme and achieve the same benefits demonstrated in

colorectal surgery. Increased familiarity with the programme and improved protocol compliance may lead to further reductions in length of stay. The ready transfer of the ERAS protocol from the colorectal practice to a hepatic resection model also suggests that the protocol is inherently robust for abdominal surgery and could be adopted more widely in General surgical practice.

ERAS Protocols are now being adapted for upper GI and pancreatic surgery (M.Braga, Italy and K Lassen, Norway, personal communication). Clearly each operative site has specific areas of concern, for example, management of feeding jejunstomies, radiological imaging of the oesophageal anastomosis in relation to restarting oral intake or use of surgical drains. Further randomised controlled trials are required to refine the ERAS protocol and the present thesis supports the continued use of a hepatic resection model in which to evaluate changes in the ERAS protocol. Due to the lack of intestinal anastomosis hepatic surgery is specifically suited to protocol elements that evaluate gastrointestinal recovery and gastrointestinal recovery is likely to be one of the main determinants of improved overall recovery.

Issues to address in future ERAS studies are both blinding of interventions and improved compliance with the postoperative protocol elements. It is not feasible to blind interventions such as mobilisation and early feeding, however, the benefit of these elements has already been accepted. The challenge is how to deliver these elements and improve patient compliance. Future studies may examine different mobilisation protocols such as more specific mobilisation targets. They may be able to introduce a dedicated physiotherapist or use of a family member or friend to act as a postoperative mobilisation coach. A tailored postoperative menu could be

employed. Smaller, more frequent meals served at patients' request may be difficult to achieve, however, serving additional nutritious snacks outwith meal times would seem an appropriate way to maximise oral intake. It is likely that within ERAS programmes both of these elements are surrogate markers for improved analgesia, reduced nausea and maintained postoperative muscle strength. Therefore poor oral intake or lack of mobilisation may in itself be a warning sign of an underlying issue such as inadequate pain control or patient nausea.

There are several issues that have delayed the adoption and implementation of the ERAS protocol. Hospital infrastructure or staffing numbers will continue to be difficult to overcome. Overcoming existing surgical doctrine and preconceptions about rate of postoperative recovery will also continue to be significant. Protocol compliance and the success of future ERAS protocols will depend on continued education of all staff members that are involved in patient care. Implementation of an ERAS programme requires a widespread dissemination of its benefits and an inclusion of all staff members that participate in the patients' perioperative journey. Education should specifically include the staff members that have most day-to-day contact with the patient. It has been previously highlighted that the patient retains ownership of their recovery, however hospital staff must also feel that they are contributing to the improvements in rate of patient recovery. It is important that all staff members that have patient contact feel part of the ERAS team. Employment of a specific specialised ERAS nurse has the benefits of allowing audit and providing an additional staff member to facilitate both dissemination of the protocol and assist in achieving compliance notably with postoperative mobilisation when lack of nursing staff may be an issue.

## 9.4 Potential role of gastric emptying rate and physical activity level as objective markers of postoperative recovery.

It is clear that current postoperative endpoints used to assess the efficacy of ERAS protocols overlap as both markers of protocol compliance and endpoints of recovery (Maessen et al, 2007). Many of the measures employed are subjective and outcomes such as length of hospital stay can be influenced by variables outwith the care pathway (Maessen et al, 2008). This thesis (Section D) presents pilot assessments of two novel markers of postoperative recovery. Both are demonstrated to be feasible in the early postoperative period and may predict a shorter or prolonged length of hospital stay.

Recovery of gastrointestinal function has been used previously as a surrogate measure of postoperative recovery in clinical trials (Avrahami et al, 1999;Lobo et al, 2002). However, the general application of this as a suitable endpoint is limited by the techniques employed to assess gastric emptying. MRI and scintigraphy can be expensive, require specialist equipment and personnel, and exposure to potentially harmful radiation. The present thesis suggests stable isotope breath testing (SIBT) as a safe and economical alternative that can be performed at the bedside. All patients that participated tolerated this test in keeping with other studies that have employed this method of assessment in children, neonates and the critically ill (Chioléro et al, 2003;Braden et al, 2004). Nine patients refused the SIBT as they found the 200ml of oral sip feed (Fortisip®, Nutricia) unpalatable and the test was also impractical for fifteen patients who had not yet been discharged from HDU as expected. Both issues that could be addressed in future studies. The correlation between patients with a

prolonged gastric emptying time and those requiring a prolonged hospital stay suggest that a delayed gastric emptying may predict a slower postoperative recovery.

There are, however, limitations with SIBT. The accuracy of this SIBT, compared to MR, may be reduced when gastric emptying is more rapid (Fruehauf et al, 2009) and optimal accuracy may depend on frequent breath samples over a prolonged period (at least six hours) (Choi et al, 1997;Choi et al, 1998;Clegg et al, 2010). Achieving this degree of accuracy in the postoperative period may make the test less desirable and it may limit both oral intake and mobilisation. It is unlikely that SIBT would be suitable to assess subtle changes in gastric emptying which may occur as a result of changes in the ERAS protocol. It is, however, a robust, easily performed test, which would be useful in identifying patients with significantly, delayed gastric emptying times (Delbende et al, 2000).

One of the limitations of the study presented in Chapter 4 was that Stable Isotope Breath Testing was performed on postoperative day 3. As patients' were usually discharged from the High Dependency Unit on day 3 this allowed easier access and space to perform the breath test. It is feasible that, at this time point, gastrointestinal function had already significantly recovered. This was a pilot study therefore the protocol and timing of the breath test was not based on any preceding data. It would be of interest to assess gastric emptying much earlier in the postoperative period (Day 1) and on repeated occasions (Days 1, 3 and 5) to assess recovery of gastric emptying rate following major abdominal surgery. Despite its limitations SIBT is one of the few techniques that could be employed to perform repeated tests in the postoperative period.

Early return to normal activity level in the postoperative period is one of the goals of the ERAS programme of care (Basse et al, 2005;Fearon et al, 2005), however, current methods of classifying postoperative activity are often subjective. The ActivPAL™ activity meter used in this thesis presents a novel and objective method of quantifying postoperative activity [Chapter 5]. The ActivPAL™ activity monitor is small and unobtrusive, it was tolerated by all of the patients who wore it and it did not hinder any of their normal activities. Unfortunately the current protocol required patients to attend hospital to have the meter activated, this resulted in a high dropout rate. The data from the activity meters highlighted the initial, rapid rise in activity level following surgery, which appeared to have settled thirty days later. Data from the activity meters (step count) appeared to correlate with length of hospital stay. Specifically those with a prolonged hospital stay (>$10^{th}$ percentile) and those with a shorter hospital stay present (<$10^{th}$ percentile). Although there was only a small number of participants in the present study there appears to be sufficient evidence to support further interest in the role of these meters.

Within the ERAS programme there is a clear question about postoperative mobilisation. Are the activity meters measuring the improved mobility of patients that have recovered more rapidly or is achieving the increased postoperative mobilisation in itself the intervention that improves rate of recovery. The activity meters can have a role in delineating this further. They would be specifically useful in comparing level of activity in the postoperative period with the level of encouragement / targets set by an individual ERAS protocol. As patients achieving a rapid recovery would be expected to mobilise more than patients whose recovery was delayed, a comparison

could be made between spontaneous, patient initiated mobilisation and activity that was initiated or supported by hospital staff as part of a protocol.

From the data presented in the present thesis (Chapter 5) activity meters can be useful in both auditing the success of postoperative mobilisation and predicting patients who are more likely to have a shorter length of hospital stay.

## 9.5 Safe administration of preoperative metabolic conditioning drinks

Despite anaesthetic guidelines prolonged preoperative fasting is still prevalent (Brady et al, 2003;Hannemann et al, 2006). In colorectal surgery this is often compounded with preoperative mechanical bowel preparation (Lassen et al, 2005;Nygren et al, 2005). Preoperative oral, liquid and carbohydrate loading facilitates a safe reduction in the fasting period (Nygren et al, 1995) and allows patients to undergo surgery in the metabolically fed state. Preoperative metabolic conditioning with 400 ml of a clear carbohydrate drink (CCD) two hours before the induction of anaesthesia, has been shown to reduce; postoperative insulin resistance, postoperative nausea and vomiting, preoperative discomfort and anxiety, and to improve patient wellbeing (Nygren et al, 1995;Hausel et al, 2001;Nygren, 2006). Chapter 6 demonstrates that preoperative carbohydrate loading and oral nutritional supplement administration can be combined with mechanical bowel preparation when required.

In the study reported in Chapter 6, 84 % of patients following an ERAS programme tolerated a regimen that combined preoperative oral fluid / CHO loading and ONS in conjunction with MBP prior to elective left colonic or rectal resection. This is in keeping with previous studies examining CHO / electrolyte replacement in conjunction with MBP prior to colonoscopy (Tjandra et al, 2004). This regimen presents a feasible method of providing the extra oral fluids required, counteracting dehydration and potentially the deleterious affects of MBP. Although the regimen presented is more complex than standard preoperative care and the protocol failed in 11 % of cases, this occurred almost exclusively with inpatients. Failure was due to the regimen not being prescribed by medical staff or not being administered by nursing staff, therefore, this is likely to improve with increased familiarity with the regimen.

Equally it reinforces the trend towards putting patients in charge and engaging them in their own care and recovery. Within a clearly defined protocol patients undergoing MBP are capable of completing a regimen of CHO / fluid loading combined with ONS, which currently is best performed as an outpatient prior to hospital admission on the day of surgery.

Within colonic resection routine administration of MBP does not reduce anastomotic leak rate (Wille-Jorgensen et al, 2003;Slim et al, 2004;Bucher et al, 2005;Ram et al, 2005;Contant et al, 2007;Jung et al, 2007). It may, however, provide a benefit in rectal resection. Although Cochrane review suggests no difference in the anastomotic leak rate when MBP was omitted prior to low anterior resections (Guenaga et al, 2009) recent evidence suggests that it may protect against anastomotic leaks requiring reoperation (Platell et al, 2006). Moreover, mechanical bowel preparation still has a role when a defunctioning ileostomy may be required, to facilitate the identification of small tumours and to allow on table colonoscopy.

There are clear benefits for patients undergoing surgery in the metabolically fed state. In the presence of MBP, where solid food is precluded, feeding can be achieved in the form of ONS and clear carbohydrate drink prior to surgery. Clearly to minimise aspiration risk it is essential to know that complete gastric emptying has occurred prior to anaesthesia. Although MR imaging has been validated against scintigraphy (Schwizer et al, 1994;Feinle et al, 1999) they differ in their assessment of gastric emptying. MR imaging measures directly the volume of gastric content. In contrast scintigraphy measures the presence of a radioactive isotope remaining in the stomach therefore MRI will account for all additional oro-gastric

secretions (Konturek et al, 1978;Taylor et al, 1982;Kidd et al, 1998). MRI is therefore the method of choice when assessing completeness of gastric emptying. For example, in relation to preoperative metabolic conditioning when it may be necessary to give a drink prior to the induction of general anaesthesia.

In Chapter 7 a novel preoperative carbohydrate drink combined with glutamine and antioxidants was assessed as it has been proposed that additional metabolic agents such as glutamine and antioxidants along with the carbohydrate may further benefit patients undergoing major abdominal surgery (Berger et al, 2007;Roth, 2008). MR imaging clearly demonstrated that these complex suspension drinks did not empty from the stomach within the two-hour time frame that was possible for the existing carbohydrate only drink. Instead it required a three-hour window. Thus the study demonstrates that it would be unsafe to give the suspension two hours prior to anaesthesia. This has major implications for the overall strategy of adding other nutrients to enhance the metabolic preparation provided by the carbohydrate load alone.

It is established that improved postoperative insulin sensitivity is dependent on surgery taking place shortly after the insulin peak provoked by the preoperative carbohydrate load. Therefore having to wait three hours or more before undertaking anaesthesia would potentially lose the benefit of the carbohydrate load within the complex preconditioning regimen. It is unclear if a delayed gastric emptying rate would delay the timing of the insulin peak or reduce its magnitude.

Further refinement of the composition of the complex drink itself may improve

gastric emptying rate and allow concurrent administration of glutamine with the preoperative carbohydrate load. It is likely, however, that the amino acid itself delays gastric emptying (Taylor et al, 1982;Kidd et al, 1998). To avoid a negative impact on the benefits of the carbohydrate load it may be that additional nutrients such as glutamine should be administered independently in the days leading up to surgery. The ERAS model of care clearly provides an ideal setting in which to evaluate both the overall benefits and the safety (gastric emptying) of such a regimen.

## 9.6 Enhanced recovery of gastrointestinal function combined with use of oral nutritional supplements and preoperative carbohydrate and fluid loading.

In this thesis it is demonstrated that, within an ERAS protocol, patients randomised to receive routine postoperative laxatives had a significantly decreased time to passage of stool after liver resection (4 (3,5) vs 5 (4,6) days: $p = 0.034$). Patients randomised to ONS showed a trend to shorter time to passage of stool (4 (3,5) vs 5 (4,7) days: $p = 0.076$) but there was no evidence of interaction between laxation and ONS [Chapter 8]. The present study was only designed to assess the individual effect of magnesium hydroxide to promote an earlier return of bowel function as marked by earlier passage of stool following surgery, therefore the number of patients in the individual subgroups was relatively small [control 19, laxation 19, supplements 15, combination of laxation and supplements 15]. However, with current data a larger study could be planned to evaluate the interaction of oral supplements and postoperative laxation with magnesium hydroxide. In the study presented here patients randomised to receive routine ONS in the early postoperative period did not intake any more calories than those who were not, in contrast with previous published studies (Stewart et al, 1998). This may account for the fact that ONS did not shorten time to recovery of gastrointestinal function and suggests that in the early postoperative phase routine ONS suppresses normal food intake to the extent that there may be no overall net benefit.

These findings are in keeping with recent trials examining the role of postoperative laxation, which highlight a hastened recovery of colonic function (first passage of stool) but no difference in tolerance of oral diet or time to hospital discharge (Hansen

et al, 2007;Zingg et al, 2008). As postoperative gastrointestinal dysfunction is one of the key causes of delayed recovery, future success of ERAS is likely to be achieved through further optimisation of early postoperative gastrointestinal function. Currently the ERAS care package (epidural, reduction in systemic opioids, restrictive IV fluid and sodium, early oral in take and mobilisation) has been shown to minimise postoperative gut dysfunction. Within traditional postoperative care no single pharmacological agents is available that has been demonstrated to further reduce postoperative gastrointestinal dysfunction. Cisparide is the only agent to have been shown to reduce postoperative ileus, however, due to cardiac side effects it is no longer available (Brown et al, 1999). Despite expectations of metoclopramide and erythromycin neither have been shown to be clinically effective (Holte et al, 2000). It is most likely that further improvement in early postoperative gastrointestinal function will rely on a combination of elements. This may consist of a prokinetic agent, such as metoclopramide to stimulate the upper GI tract and a laxative (magnesium hydroxide) to promote early colonic function. The interaction with ONS also needs further study as mentioned above.

Within the present thesis the role of postoperative magnesium hydroxide was examined within an ERAS package of care, which included epidural analgesia and avoidance of systemic opiates. Epidural analgesia may not be appropriate or desirable in all patients and systemic opiates may be required (Levy et al, 2011). In such a group of patients the potential benefit of routine laxation may be more significant. The study design in Chapter 8 specifically chose a model without colorectal anastomosis, however, there is no evidence that postoperative laxatives increase the risk of postoperative anastomotic leak (Basse et al, 2000;Zingg et al, 2008).

Systemic opiate dose has been shown to correlate with recovery of bowel function (Cali et al, 2000) and as such within ERAS protocols an opiate-sparing regimen is employed. Selective peripherally acting μ-receptor antagonists and K-receptor agonists have been shown to reduce this opiate induced postoperative ileus (Rivière et al, 1993). Currently these agents are expensive and their use limited in the postoperative period. One commercially available preparation Targinact® combines an oral opioid (oxycodone) with naloxone (μ-receptor antagonists). Naloxone has been show to reverse the negative gastrointestinal effect of opioids, however, as it crosses the blood brain barrier and therefore can also reverse the analgesic effect of opioids. As an oral preparation first pass metabolism is estimated at 97% therefore restricting its action to the bowel itself. This may be suited to patients requiring systemic opioids specifically those not suitable for epidural analgesia. Alvimopan, (another μ-receptor antagonists) does not cross the blood-brain barrier and has been shown to reduce time to gastrointestinal recovery after open colorectal resection (Ludwig et al, 2008). Further combination with laxatives may be interesting. Combining this agent or other K-receptor agonists such as Asimadoline or Fedotozine with the ERAS package of care may reduce postoperative gastrointestinal dysfunction (specifically opiate related ileus). As part of such a package the addition of a laxative may again be more significant, specifically with respect to improved outcomes such as increased calorie intake or earlier functional recovery.

The overall outcomes documented in Chapter 8 of the present thesis further demonstrate the benefit of an ERAS package of care for patients undergoing liver resection. Patients recommenced oral fluid intake on the day of surgery, started eating

the day after surgery and were mobile by the third postoperative day. Functional recovery was achieved a median of four days following surgery and overall median hospital stay was six days, which is shorter than the 8-14 days reported in other centres following a traditional care (Jarnagin et al, 2002;Dimick et al, 2004;Capussotti et al, 2006;Petrowsky et al, 2006). Morbidity rates were lower and mortality rates in keeping with those published from other countries following traditional care pathways (38 – 45 % and 2.7 – 3.1 % respectively) (Jarnagin et al, 2002;Petrowsky et al, 2006;Nikfarjam et al, 2009).

Compliance with postoperative elements of the protocol remains an area of difficulty, specifically mobilisation in the early postoperative period. In the study presented in Chapter 8 only 28 % of patients mobilised on the day of surgery. The delay in mobilisation was often attributed to a delayed return from theatre recovery, lack of ward staff or epidural-related hypotension. It is desirable that patients following an ERAS protocol are placed first on an operating. There are, however, competing interests for this position and undergoing surgery later in the day should not preclude participation in an ERAS programme. Mobilisation could begin in theatre recovery if a protracted stay is expected. Increase familiarity with ambulatory epidurals and availability of medical staff with an expertise in managing epidural analgesia is likely to be the most effective method of maintaining effective analgesia and minimising side effects such as postural hypotension. Within the study presented in Chapter 8 oral ephedrine was employed prior to mobilisation but careful monitoring of fluid balance is also required. The availability of a dedicated ERAS nurse may provide the extra support and manpower required to encourage mobilisation for the first time after surgery. It is still viewed as a labour intensive action and if the high dependency ward

is busy it is likely that encouraging and assisting ERAS patients to mobilise may be neglected. A staff member dedicated to implementing the ERAS protocol may provide the relevant manpower to ensure postoperative elements such as early mobilisation are not neglected.

Previous ERAS studies have highlighted a delay in hospital discharge beyond functional recovery (Maessen et al, 2008). This is again apparent in chapter 8 where hospital stay was a median of 2 days beyond achievement of functional recovery. Removing this delay would allow a significant reduction in length of hospital stay. There will continue to be social issues associated with certain groups of patients, which can often frustrate hospital discharge. To overcome this forward discharge planning should take place. Patients likely to require additional help at home should be highlighted and suitable support organised before functional recovery is complete. This has already been highlighted as an area of significance, independently of the ERAS programme and has been shown to reduce patients stay and with improved patients satisfaction though mainly in medical patients (Shepperd et al, 2004).

Within Chapter 8 the main reasons for this delay beyond achieving discharge criteria were that the patient did not feel ready or that medical staff had concerns related to earlier complications. Continued education of both patients and medical staff may provide the key to reduce this delay. The ERAS protocol is likely to be the first occasion in which a written discharge criteria is presented to doctors, nurses and patients. Outwith this protocol, readiness for discharge is subjective. Continued education will serve to change expectations of required length of hospital stay and improved familiarity with the protocol and audit of patient outcomes will serve to

reassure medical staff of the safety of discharging patients 'as per protocol' as soon as functional recovery is achieved. The overall success of the ERAS protocol will be improved by the effective dissemination of ERAS protocol. Hospital staff and patients must feel that they have an ownership both of the protocol and the results

## 9.7 Summary of conclusions

The present thesis adds to the growing evidence supporting Enhanced Recovery After Surgery protocols and their application to all patients undergoing major abdominal surgery. It highlights the benefits for high-risk surgical patients (undernourished and elderly) undergoing colorectal resection and the improved outcomes for patients undergoing hepatic surgery within such a protocol. The ability of the ERAS protocol to adapt to variations in practice is also highlighted through the feasibility of carbohydrate / fluid loading in spite of preoperative mechanical bowel preparation.

The main study presented in the present thesis [Chapter 8] demonstrates that within an ERAS protocol of care routine laxation with magnesium hydroxide results in an earlier recovery of colonic function (passage of stool). Although this study did not demonstrate any further improvement in functional recovery (earlier achievement of meeting discharge criteria or discharge form hospital) previous studies have highlighted a link between both time to passage of stool / tolerance of oral diet and length of hospital stay (Delaney et al, 2006). Therefore, return of colonic function may represent half of the equation to achieve earlier functional recovery and future studies should aim to combine the success of this study with protocol elements that target improved calorie intake in the early postoperative period.

The randomised trial in this thesis also presents a model, which can be utilised to assess the individual contribution of protocol elements towards the overall benefits achieved with ERAS. The feasibility of new, objective outcome measures (gastric emptying and postoperative activity level) have been demonstrated and appear to

show correlation with other traditional markers of recovery. These show promise as objective markers of recovery for future studies.

The ERAS package of care provides support to the surgical patient through every aspect of their journey from hospital entrance to hospital exit and importantly returns ownership of recovery back to the patient on departure from the operating room. Overall it has been shown to be robust and applicable to different domains of major abdominal surgery. Its benefits are applicable to all patients including those traditionally considered high-risk. It is adaptable and evolves to include surgical advances such as minimal access surgery, where appropriate further benefit is demonstrated. It must continue to be combined with audit of protocol compliance and significant objective outcomes notably postoperative morbidity, activity and nutrition. Where possible more objective markers of physiological and gastrointestinal recovery should be further refined for this group.

In the surgical department there is a common goal of safely shortening postoperative recovery time. The ERAS pathway provides a safe method of achieving this and hastening return to preoperative functional level. These protocols are streamlined and patient centred and in many centres it represents the most accessible dissemination of evidence-based practice to medical, nursing and auxiliary staff. Enhanced Recovery After Surgery provides state of the art perioperative care for patients resulting in a faster postoperative recovery, reduced length of hospital stay and reduced consumption of resources. It incorporates the evolving evidence base and rejects outdated, unfounded surgical doctrine and will therefore continue to improve outcomes for patients no matter the future direction of the practice of surgery.

# Appendices

## Appendix A Nutritional composition of 200 ml Nutricia Fortisip test feed

| | |
|---|---|
| Volume (ml) | 200 |
| Energy (Kcal) | 300 |
| Protein (g) | 12 |
| Fat (g) | 11.6 |
| Carbohydrate(g) | 36.8 |
| Vitamin A (mcg) | 246 |
| Carotenoids (mg) | 0.60 |
| Viramin D (mcg) | 2.2 |
| Vitamin E (mg) | 3.8 |
| Vitamin K (mcg) | 16 |
| Vitamin C (mg) | 30 |
| Thiamin (mg) | 0.46 |
| Riboflavin (mg) | 0.48 |
| Niacin (mg) | 5.2 |
| Vitamin B6 (mg) | 0.52 |
| Vitamin B12 (mcg) | 0.64 |
| Folic Acid (mcg) | 80 |
| Pantothenic Acid (mg) | 1.6 |
| Biotin (mcg) | 12 |
| Sodium (mg/mmol) | 180 / 7.8 |
| Potassium (mg/mmol) | 318 / 8.2 |
| Chloride (mg/mmol) | 174 / 5 |
| Calcium (mg) | 182 |
| Phosphorus (mg) | 156 |
| Magnesium (mg) | 46 |
| Iron (mg) | 4.8 |
| Zinc (mg) | 3.6 |
| Manganese (mg) | 46 |
| Copper (mcg) | 540 |
| Iodine (mcg) | 40 |
| Molybdenum (mcg) | 30 |
| Selenium (mcg) | 17.2 |
| Chromium (mcg) | 20 |
| Fluoride (mg) | 0.3 |
| Choline (mg) | 110 |
| Water (g) | 156 |
| Osmolality (mOsm/kg) | 590 |
| Potential renal solute load (mOsm/l) | 465 |
| pH | 6.9 |
| Viscosity (mPa.s) | 20 |

## *REFERENCES*


Abraham NS, Young JM, Solomon MJ. Meta-analysis of short-term outcomes after laparoscopic resection for colorectal cancer. Br J Surg. 2004 Sep 1;91(9):1111-24.

Alley PG. Surgery for colorectal cancer in elderly patients. Lancet. 2000 Sep 16;356(9234):956.

Alves A, Panis Y, Mathieu P, Mantion G, Kwiatkowski F, Slim K. Postoperative mortality and morbidity in French patients undergoing colorectal surgery: results of a prospective multicenter study. Arch Surg. 2005 Mar;140(3):278-83, discussion 84.

American Society of Anesthesiologists. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: a report by the American Society of Anesthesiologist Task Force on Preoperative Fasting. Anesthesiology. 1999 Mar 1;90(3):896-905.

Andersen HK, Lewis SJ, Thomas S. Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications. Cochrane Database Syst Rev. 2006(4):CD004080.

Andersen J, Hjort-Jakobsen D, Christiansen PS, Kehlet H. Readmission rates after a planned hospital stay of 2 versus 3 days in fast-track colonic surgery. Br J Surg. 2007 Jul 1;94(7):890-3.

Anderson AD, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. Br J Surg. 2003 12;90(12):1497-504.

Apfel CC, Kranke P, Eberhart LHJ, Roos A, Roewer N. Comparison of predictive models for postoperative nausea and vomiting. Br J Anaesth. 2002 Feb 1;88(2):234-40.

Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. Am Rev Respir Dis. 1982 Jul;126(1):5-8.

Avrahami R, Cohen JD, Haddad M, Singer P, Zelikovski A. Gastric emptying after elective abdominal aortic aneurysm surgery: the case for early postoperative enteral feeding. Eur J Vasc Endovasc Surg. 1999 Mar 1;17(3):241-4.

Awad S, Constantin-Teodosiu D, Constantin D, Rowlands BJ, Fearon KCH, Macdonald IA, Lobo DN. Cellular mechanisms underlying the protective effects of preoperative feeding: a randomized study investigating muscle and liver glycogen content, mitochondrial function, gene and protein expression. Ann Surg. [Randomized Controlled Trial]. 2010 Aug;252(2):247-53.

BAPEN. Malnutrition Universal Screening Tool: Malnutrition Advisory Group2003 2003.

Basse L, Hjort Jakobsen D, Billesbølle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. Ann Surg. 2000 Jul 1;232(1):51-7.

Basse L, Jakobsen DH, Bardram L, Billesbølle P, Lund C, Mogensen T, Rosenberg J, Kehlet H. Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study. Ann Surg. 2005 Mar 1;241(3):416-23.

Basse L, Raskov HH, Hjort Jakobsen D, Sonne E, Billesbølle P, Hendel HW, Rosenberg J, Kehlet H. Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. Br J Surg. 2002 Apr 1;89(4):446-53.

Basse L, Thorbøl JE, Løssl K, Kehlet H. Colonic surgery with accelerated rehabilitation or conventional care. Dis Colon Rectum. 2004 Mar 1;47(3):271-7; discussion 7-8.

Basse L, Werner M, Kehlet H. Is urinary drainage necessary during continuous epidural analgesia after colonic resection? Reg Anesth Pain Med. 2000 09;25(5):498-501.

Beale RJ, Bryg DJ, Bihari DJ. Immunonutrition in the critically ill: a systematic review of clinical outcome. Crit Care Med. [Meta-Analysis]. 1999 Dec;27(12):2799-805.

Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. Gut. 2000 06;46(6):813-8.

Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg. 2000 Jul 1;191(1):38-46.

Benzoni E, Cojutti A, Lorenzin D, Adani GL, Baccarani U, Favero A, Zompicchiati A, Bresadola F, Uzzau A. Liver resective surgery: a multivariate analysis of postoperative outcome and complication. Langenbecks Arch Surg. 2007 Jan 1;392(1):45-54.

Berger MM, Chioléro RL. Antioxidant supplementation in sepsis and systemic inflammatory response syndrome. Crit Care Med. 2007 Sep 1;35(9 Suppl):S584-90.

Bessey PQ, Lowe KA. Early hormonal changes affect the catabolic response to trauma. Ann Surg. 1993 Oct 1;218(4):476-89; discussion 89-91.

Bessey PQ, Watters JM, Aoki TT, Wilmore DW. Combined hormonal infusion simulates the metabolic response to injury. Ann Surg. 1984 Sep 1;200(3):264-81.

Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA. 2003 Nov 12;290(18):2455-63.

Bluck LJ, Coward WA. Measurement of gastric emptying by the 13C-octanoate breath test--rationalization with scintigraphy. Physiol Meas. 2006 Mar 1;27(3):279-89.

Bokey EL, Chapuis PH, Fung C, Hughes WJ, Koorey SG, Brewer D, Newland RC. Postoperative morbidity and mortality following resection of the colon and rectum for cancer. Dis Colon Rectum. 1995 May 1;38(5):480-6; discussion 6-7.

Botella-Carretero JI, Iglesias B, Balsa JA, Zamarrón I, Arrieta F, Vázquez C. Effects of oral nutritional supplements in normally nourished or mildly undernourished geriatric patients after surgery for hip fracture: a randomized clinical trial. Journal of Parenteral and Enteral Nutrition. 2008 Jan 1;32(2):120-8.

Boulby P, Gowland P, Adams V, Spiller RC. Use of echo planar imaging to demonstrate the effect of posture on the intragastric distribution and emptying of an oil/water meal. Neurogastroenterol Motil. 1997 Mar 1;9(1):41-7.

Bowles TA, Sanders KM, Colson M, Watters DA. Simplified risk stratification in elective colorectal surgery. Aust N Z J Surg. 2008 Jan-Feb;78(1-2):24-7.

Braden B, Adams S, Duan LP, Orth KH, Maul FD, Lembcke B, Hör G, Caspary WF. The [13C]acetate breath test accurately reflects gastric emptying of liquids in both liquid and semisolid test meals. Gastroenterology. 1995 Apr 1;108(4):1048-55.

Braden B, Peterknecht A, Piepho T, Schneider A, Caspary WF, Hamscho N, Ahrens P. Measuring gastric emptying of semisolids in children using the 13C-acetate breath test: a validation study. Dig Liver Dis. 2004 Apr 1;36(4):260-4.

Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications. Cochrane Database Syst Rev. 2003 Jan 1(4):CD004423.

Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. Archives of surgery (Chicago, Ill : 1960). [Clinical Trial]. 2002 Mar;137(2):174-80.

Braga M, Gianotti L, Radaelli G, Vignali A, Mari G, Gentilini O, Di Carlo V. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. Arch Surg. 1999 Apr 1;134(4):428-33.

Braga M, Gianotti L, Vignali A, Carlo VD. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. Surgery. [Clinical Trial]. 2002 Nov;132(5):805-14.

Braga M, Vignali A, Gianotti L, Zuliani W, Radaelli G, Gruarin P, Dellabona P, Di Carlo V. Laparoscopic versus open colorectal surgery: a randomized trial on short-term outcome. Ann Surg. 2002 Dec;236(6):759-66; disscussion 67.

Brandstrup B, Tønnesen H, Beier-Holgersen R, Hjortsø E, Ørding H, Lindorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH, Gramkow CS, Okholm M,

Blemmer T, Svendsen P-E, Rottensten HH, Thage B, Riis J, Jeppesen IS, Teilum D, Christensen AM, Graungaard B, Pott F, Therapy DSGoPF. Effects of Intravenous Fluid Restriction on Postoperative Complications: Comparison of Two Perioperative Fluid Regimens. Ann Surg. 2003 Nov 1;238(5):641-8.

Bratten J, Jones MP. New directions in the assessment of gastric function: clinical applications of physiologic measurements. Dig Dis. 2006 Jan 1;24(3-4):252-9.

Bretagnol F, Alves A, Ricci A, Valleur P, Panis Y. Rectal cancer surgery without mechanical bowel preparation. Br J Surg. 2007 Oct 1;94(10):1266-71.

Breuer JP, von Dossow V, von Heymann C, Griesbach M, von Schickfus M, Mackh E, Hacker C, Elgeti U, Konertz W, Wernecke KD, Spies CD. Preoperative oral carbohydrate administration to ASA III-IV patients undergoing elective cardiac surgery. Anesth Analg. 2006 Nov 1;103(5):1099-108.

Brown SR, Goodfellow PB. Transverse verses midline incisions for abdominal surgery. Cochrane Database Syst Rev. 2005 Feb 01(4):CD005199.

Brown TA, McDonald J, Williard W. A prospective, randomized, double-blinded, placebo-controlled trial of cisapride after colorectal surgery. Am J Surg. 1999 May 1;177(5):399-401.

Bruce D, Laurance I, McGuiness M, Ridley M, Goldswain P. Nutritional supplements after hip fracture: poor compliance limits effectiveness. Clin Nutr. 2003 Oct 1;22(5):497-500.

Brunetto AL, Pearson AD, Gibson R, Bateman DN, Rashid MU, Laker MF. The effect of pharmacological modification of gastric emptying and mouth-to-caecum transit time on the absorption of sugar probe marker molecules of intestinal permeability in normal man. Eur J Clin Invest. 1990 Jun 1;20(3):279-84.

Bucher P, Gervaz P, Soravia C, Mermillod B, Erne M, Morel P. Randomized clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery. Br J Surg. 2005 04;92(4):409-14.

Burns LR, Wholey DR. The effects of patient, hospital, and physician characteristics on length of stay and mortality. Med Care. 1991 Mar 1;29(3):251-71.

Burt BM, Brown K, Jarnagin W, DeMatteo R, Blumgart LH, Fong Y. An audit of results of a no-drainage practice policy after hepatectomy. Am J Surg. 2002 11;184(5):441-5.

Cali RL, Meade PG, Swanson MS, Freeman C. Effect of Morphine and incision length on bowel function after colectomy. Dis Colon Rectum. 2000 Feb 1;43(2):163-8.

Capussotti L, Muratore A, Ferrero A, Massucco P, Ribero D, Polastri R. Randomized clinical trial of liver resection with and without hepatic pedicle clamping. Br J Surg. 2006 Jun 1;93(6):685-9.

Catchpole BN. Smooth muscle and the surgeon. Aust N Z J Surg. 1989 Mar 1;59(3):199-208.

Cerfolio RJ, Bryant AS, Bass CS, Alexander JR, Bartolucci AA. Fast tracking after Ivor Lewis esophagogastrectomy. Chest. 2004 10;126(4):1187-94.

Charoenkwan K, Phillipson G, Vutyavanich T. Early versus delayed (traditional) oral fluids and food for reducing complications after major abdominal gynaecologic surgery. Cochrane Database Syst Rev. 2007 Jan 1(4):CD004508.

Cheatham ML, Chapman WC, Key SP, Sawyers JL. A meta-analysis of selective versus routine nasogastric decompression after elective laparotomy. Ann Surg. 1995 05;221(5):469-76.

Chioléro RL, Revelly J-P, Berger MM, Cayeux M-C, Schneiter P, Tappy L. Labeled acetate to assess intestinal absorption in critically ill patients. Crit Care Med. 2003 Mar 1;31(3):853-7.

Choi MG, Camilleri M, Burton DD, Zinsmeister AR, Forstrom LA, Nair KS. [13C]octanoic acid breath test for gastric emptying of solids: accuracy, reproducibility, and comparison with scintigraphy. Gastroenterology. 1997 Apr 1;112(4):1155-62.

Choi MG, Camilleri M, Burton DD, Zinsmeister AR, Forstrom LA, Nair KS. Reproducibility and simplification of 13C-octanoic acid breath test for gastric emptying of solids. Am J Gastroenterol. 1998 Jan 1;93(1):92-8.

Clegg ME, Shafat A. Procedures in the 13C octanoic acid breath test for measurement of gastric emptying: analysis using Bland-Altman methods. Scand J Gastroenterol. 2010 Aug;45(7-8):852-61.

Cochrane JP, Forsling ML, Gow NM, Le Quesne LP. Arginine vasopressin release following surgical operations. Br J Surg. 1981 Mar 1;68(3):209-13.

Contant CM, Hop WC, van't Sant HP, Oostvogel HJ, Smeets HJ, Stassen LP, Neijenhuis PA, Idenburg FJ, Dijkhuis CM, Heres P, van Tets WF, Gerritsen JJ, Weidema WF. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. Lancet. 2007 Dec 22;370(9605):2112-7.

Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. Br J Surg. 1991 03;78(3):355-60.

Cuthbertson DP. The disturbance of metabolism produced by bony and non-bony injury, with notes on certain abnormal conditions of bone. Biochem J. 1930 Jan 1;24(4):1244-63.

Cuthbertson DP. The distribution of nitrogen and sulphur in the urine during conditions of increased catabolism. Biochem J. 1931 Jan 1;25(1):236-44.

Dahele M, Skipworth R, Wall L, Voss A, Preston T, Fearon K. Objective Physical Activity and Self-Reported Quality of Life in Patients Receiving Palliative Chemotherapy. J Pain Symptom Manage. 2007 Jun 1;33(6):676-85.

Datz FL, Christian PE, Moore J. Gender-related differences in gastric emptying. J Nucl Med. 1987 Jul 1;28(7):1204-7.

Déchelotte P, Hasselmann M, Cynober L, Allaouchiche B, Coëffier M, Hecketsweiler B, Merle V, Mazerolles M, Samba D, Guillou YM, Petit J, Mansoor O, Colas G, Cohendy R, Barnoud D, Czernichow P, Bleichner G. L-alanyl-L-glutamine dipeptide-supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: the French controlled, randomized, double-blind, multicenter study. Crit Care Med. [Multicenter Study]. 2006 Apr;34(3):598-604.

Degen LP, Phillips SF. Variability of gastrointestinal transit in healthy women and men. Gut. 1996 Aug 1;39(2):299-305.

Delaney CP, Senagore AJ, Viscusi ER, Wolff BG, Fort J, Du W, Techner L, Wallin B. Postoperative upper and lower gastrointestinal recovery and gastrointestinal morbidity in patients undergoing bowel resection: pooled analysis of placebo data from 3 randomized controlled trials. Am J Surg. 2006 Mar 1;191(3):315-9.

Delbende B, Perri F, Couturier O, Leodolter A, Mauger P, Bridgi B, Bizais Y, des Varannes SB, Andriulli A, Galmiche JP. 13C-octanoic acid breath test for gastric emptying measurement. Eur J Gastroenterol Hepatol. 2000 Jan 1;12(1):85-91.

Desborough JP. The stress response to trauma and surgery. Br J Anaesth. 2000 Jul;85(1):109-17.

Dimick JB, Wainess RM, Cowan JA, Upchurch GR, Knol JA, Colletti LM. National trends in the use and outcomes of hepatic resection. J Am Coll Surg. 2004 Jul 1;199(1):31-8.

Disbrow EA, Bennett HL, Owings JT. Effect of preoperative suggestion on postoperative gastrointestinal motility. West J Med. 1993 05;158(5):488-92.

Egbert LD, Battit GE, Welch CE, Bartlett MK. Reduction of Postoperative Pain by Encouragement and Instruction of Patients. a Study of Doctor-Patient Rapport. N Engl J Med. 1964 Apr 16;270:825-7.

Egdahl RH. Pituitary-adrenal response following trauma to the isolated leg. Surgery. 1959 Jul 1;46(1):9-21.

Epstein AM, Stern RS, Tognetti J, Begg CB, Hartley RM, Cumella E, Ayanian JZ. The association of patients' socioeconomic characteristics with the length of hospital stay and hospital charges within diagnosis-related groups. N Engl J Med. 1988 Jun 16;318(24):1579-85.

Ergina PL, Gold SL, Meakins JL. Perioperative care of the elderly patient. World J Surg. 1993 Jan 1;17(2):192-8.

Fanning J, Yu-Brekke S. Prospective trial of aggressive postoperative bowel stimulation following radical hysterectomy. Gynecol Oncol. 1999 06;73(3):412-4.

Fazio V, Tekkis P, Remzi F, Lavery I. Assessment of Operative Risk in Colorectal Cancer Surgery: The Cleveland Clinic Foundation Colorectal Cancer Model. Dis Colon Rectum. 2004 Dec 26;47(12):2015-24.

Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, Nygren J, Hausel J, Soop M, Andersen J, Kehlet H. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr. 2005 Jun;24(3):466-77.

Feinle C, Kunz P, Boesiger P, Fried M, Schwizer W. Scintigraphic validation of a magnetic resonance imaging method to study gastric emptying of a solid meal in humans. Gut. 1999 Jan 1;44(1):106-11.

Feo CV, Romanini B, Sortini D, Ragazzi R, Zamboni P, Pansini GC, Liboni A. Early oral feeding after colorectal resection: a randomized controlled study. Aust N Z J Surg. 2004 May 1;74(5):298-301.

Figueras J, Llado L, Miro M, Ramos E, Torras J, Fabregat J, Serrano T. Application of fibrin glue sealant after hepatectomy does not seem justified: results of a randomized study in 300 patients. Ann Surg. 2007 Apr 1;245(4):536-42.

Fong Y, Brennan MF, Brown K, Heffernan N, Blumgart LH. Drainage is unnecessary after elective liver resection. Am J Surg. 1996 01;171(1):158-62.

Forster AJ, Clark HD, Menard A, Dupuis N, Chernish R, Chandok N, Khan A, Letourneau M, van Walraven C. Effect of a nurse team coordinator on outcomes for hospitalized medicine patients. Am J Med. 2005 Oct 1;118(10):1148-53.

Fotiadis RJ, Badvie S, Weston MD, len-Mersh TG. Epidural analgesia in gastrointestinal surgery. Br J Surg. 2004 07;91(7):828-41.

Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KF, Kelly S, Beattie C. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. JAMA. 1997 04/09/;277(14):1127-34.

Fruehauf H, Steingoetter A, Fox MR, Kwiatek MA, Boesiger P, Schwizer W, Fried M, Thumshirn M, Goetze O. Characterization of gastric volume responses and liquid emptying in functional dyspepsia and health by MRI or barostat and simultaneous C-acetate breath test. Neurogastroenterol Motil. 2009 Jul 01;21(7):697-e37.

Gatt M, Anderson AD, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J. Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. Br J Surg. 2005 11;92(11):1354-62.

Gianotti L, Braga M, Nespoli L, Radaelli G, Beneduce A, Di Carlo V. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients

with gastrointestinal cancer. Gastroenterology. [Clinical Trial]. 2002 Jul;122(7):1763-70.

Giner M, Laviano A, Meguid MM, Gleason JR. In 1995 a correlation between malnutrition and poor outcome in critically ill patients still exists. Nutrition. 1996 Jan;12(1):23-9.

Guenaga KF, Matos D, Castro AA, Atallah AN, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane database of systematic reviews (Online). 2005 Feb 01(1):CD001544.

Guenaga KK, Matos D, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2009 Jan 1(1):CD001544.

Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM, group MCt. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet. 2005 Jan 1;365(9472):1718-26.

Gustafsson UO, Nygren J, Thorell A, Soop M, Hellström PM, Ljungqvist O, Hagström-Toft E. Pre-operative carbohydrate loading may be used in type 2 diabetes patients. Acta Anaesthesiol. 2008 Aug 1;52(7):946-51.

Halaszynski TM, Juda R, Silverman DG. Optimizing postoperative outcomes with efficient preoperative assessment and management. Crit Care Med. 2004 Apr 1;32(4 Suppl):S76-86.

Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. J Am Geriatr Soc. 2005 Mar;53(3):424-9.

Han-Geurts I, Hop W, Kok N, Lim A, Brouwer K, Jeekel J. Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery. Br J Surg. 2007 May 1;94(5):555-61.

Hannemann P, Lassen K, Hausel J, Nimmo S, Ljungqvist O, Nygren J, Soop M, Fearon K, Andersen J, Revhaug A, von Meyenfeldt MF, Dejong CH, Spies C. Patterns in current anaesthesiological peri-operative practice for colonic resections: a survey in five northern-European countries. Acta Anaesthesiol. 2006 Oct 1;50(9):1152-60.

Hansen CT, Sorensen M, Moller C, Ottesen B, Kehlet H. Effect of laxatives on gastrointestinal functional recovery in fast-track hysterectomy: a double-blind, placebo-controlled randomized study. Am J Obstet Gynecol. 2007 Apr;196(4):311 e1-7.

Hausel J, Nygren J, Lagerkranser M, Hellström PM, Hammarqvist F, Almström C, Lindh A, Thorell A, Ljungqvist O. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. Anesth Analg. 2001 Nov 1;93(5):1344-50.

Hausel J, Nygren J, Thorell A, Lagerkranser M, Ljungqvist O. Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy. Br J Surg. 2005 Apr 1;92(4):415-21.

Hellström PM, Grybäck P, Jacobsson H. The physiology of gastric emptying. Best Pract Res Clin Anaesthesiol. 2006 Sep 1;20(3):397-407.

Henriksen MG, Jensen MB, Hansen HV, Jespersen TW, Hessov I. Enforced mobilization, early oral feeding, and balanced analgesia improve convalescence after colorectal surgery. Nutrition. 2002 02;18(2):147-52.

Heriot AG, Tekkis PP, Smith JJ, Cohen CR, Montgomery A, Audisio RA, Thompson MR, Stamatakis JD. Prediction of postoperative mortality in elderly patients with colorectal cancer. Dis Colon Rectum. 2006 Jun 1;49(6):816-24.

Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA: The Journal of the American Medical Association. [Meta-Analysis]. 2001 Jul;286(8):944-53.

Heys SD, Walker LG, Smith I, Eremin O. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. Ann Surg. [Comparative Study]. 1999 May;229(4):467-77.

Hill AG. Initiators and propagators of the metabolic response to injury. World J Surg. 2000 Jun 1;24(6):624-9.

Hill GL. Impact of nutritional support on the clinical outcome of the surgical patient. Clin Nutr. 1994 Dec;13(6):331-40.

Hjort Jakobsen D, Sonne E, Basse L, Bisgaard T, Kehlet H. Convalescence after colonic resection with fast-track versus conventional care. Scand J Surg. 2004 Jan 1;93(1):24-8.

Holte K, Foss NB, Svensén C, Lund C, Madsen JL, Kehlet H. Epidural anesthesia, hypotension, and changes in intravascular volume. Anesthesiology. 2004 Feb 1;100(2):281-6.

Holte K, Kehlet H. Postoperative ileus: a preventable event. Br J Surg. 2000 Nov 1;87(11):1480-93.

Holte K, Kehlet H. Postoperative ileus: progress towards effective management. Drugs. 2002 Jan 1;62(18):2603-15.

Horowitz M, Dent J, Fraser R, Sun W, Hebbard G. Role and integration of mechanisms controlling gastric emptying. Dig Dis Sci. 1994 Dec 1;39(12 Suppl):7S-13S.

Houdijk AP, Rijnsburger ER, Jansen J, Wesdorp RI, Weiss JK, McCamish MA, Teerlink T, Meuwissen SG, Haarman HJ, Thijs LG, van Leeuwen PA. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet. [Clinical Trial]. 1998 Sep 05;352(9130):772-6.

Hustvedt B-E, Christophersen A, Johnsen LR, Tomten H, McNeill G, Haggarty P, Løvø A. Description and validation of the ActiReg: a novel instrument to measure physical activity and energy expenditure. Br J Nutr. 2004 Dec 1;92(6):1001-8.

Ingle DJ, Ward EO, Kuizenga MH. The relationship of the adrenal glands to changes in urinary non-protein nitrogen following multiple fractures in the force-fed rat. Am J Physiol. 1947 May 1;149(2):510-5.

International Hepato-Pacreato-Biiary Association. Terminology of liver anatomy and resections. HPB Surg. 2000;2:333-9.

Jakobsen DH, Sonne E, Andreasen J, Kehlet H. Convalescence after colonic surgery with fast-track vs conventional care. Colorectal Dis. 2006 Oct 1;8(8):683-7.

Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, Corvera C, Weber S, Blumgart LH. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg. 2002 Oct 1;236(4):397-406; discussion -7.

Jesus EC, Karliczek A, Matos D, Castro AA, Atallah AN. Prophylactic anastomotic drainage for colorectal surgery. Cochrane Database Syst Rev. 2004(4):CD002100.

Jiang K, Cheng L, Wang J-J, Li J-S, Nie J. Fast track clinical pathway implications in esophagogastrectomy. World J Gastroenterol. 2009 Jan 28;15(4):496-501.

Jones C, Palmer TE, Griffiths RD. Randomized clinical outcome study of critically ill patients given glutamine-supplemented enteral nutrition. Nutrition (Burbank, Los Angeles County, Calif). [Clinical Trial]. 1999 Mar;15(2):108-15.

Jörgen N, Björn N, Tomas S, Wahrenberg H, Peter A. Catecholamine regulation of adipocyte lipolysis after surgery. Surgery. 1991 Apr 1;109(4):488-96.

Jørgensen H, Wetterslev J, Møiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev. 2000 Jan 1(4):CD001893.

Jung B, Påhlman L, Nyström PO, Nilsson E, Group MBPS. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Br J Surg. 2007 Jun 1;94(6):689-95.

Kalff JC, Schraut WH, Simmons RL, Bauer AJ. Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. Ann Surg. 1998 Nov 1;228(5):652-63.

Karliczek A, Jesus EC, Matos D, Castro AA, Atallah AN, Wiggers T. Drainage or nondrainage in elective colorectal anastomosis: a systematic review and meta-analysis. Colorectal Dis. 2006 May 1;8(4):259-65.

Keele AM, Bray MJ, Emery PW, Duncan HD, Silk DB. Two phase randomised controlled clinical trial of postoperative oral dietary supplements in surgical patients. Gut. 1997 03;40(3):393-9.

Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth. 1997 05;78(5):606-17.

Kehlet H. Fast-track colorectal surgery. Lancet. 2008 Mar 8;371(9615):791-3.

Kehlet H, Büchler MW, Beart RW, Billingham RP, Williamson R. Care after colonic operation--is it evidence-based? Results from a multinational survey in Europe and the United States. J Am Coll Surg. 2006 Jan 1;202(1):45-54.

Kehlet H, Holte K. Review of postoperative ileus. Am J Surg. 2001 Nov 1;182(5A Suppl):3S-10S.

Kehlet H, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. Br J Surg. 1999 Feb 1;86(2):227-30.

Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002 Jun;183(6):630-41.

Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. Ann Surg. 2007 Jun 1;245(6):867-72.

Kidd M, Modlin IM, Tang LH. Gastrin and the enterochromaffin-like cell: an acid update. Dig Surg. 1998 Jan 1;15(3):209-17.

Kiecolt-Glaser JK, Page GG, Marucha PT, MacCallum RC, Glaser R. Psychological influences on surgical recovery. Perspectives from psychoneuroimmunology. The American psychologist. 1998 Nov 1;53(11):1209-18.

King PM, Blazeby JM, Ewings P, Franks PJ, Longman RJ, Kendrick AH, Kipling RM, Kennedy RH. Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. Br J Surg. 2006 Mar 1;93(3):300-8.

King PM, Blazeby JM, Ewings P, Kennedy RH. Detailed evaluation of functional recovery following laparoscopic or open surgery for colorectal cancer within an enhanced recovery programme. Int J Colorectal Dis. 2008 May 9.

Kinney JM, Elwyn DH. Protein metabolism and injury. Annu Rev Nutr. 1983 Jan 1;3:433-66.

Kong MF, Horowitz M. Diabetic gastroparesis. Diabet Med. 2005 Sep 1;22 Suppl 4:13-8.

Konturek SJ, Kwiecień N, Obtułowicz W, Mikoś E, Sito E, Oleksy J. Comparison of intraduodenal and intravenous administration of amino acids on gastric secretion in healthy subjects and patients with duodenal ulcer. Gut. 1978 Oct 1;19(10):859-64.

Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med. 1996 05/09/;334(19):1209-15.

Lang M, Niskanen M, Miettinen P, Alhava E, Takala J. Outcome and resource utilization in gastroenterological surgery. Br J Surg. 2001 Jul;88(7):1006-14.

Lassen K, Hannemann P, Ljungqvist O, Fearon K, DeJong CH, von Meyenfeldt MF, Hausel J, Nygren J, Andersen J, Revhaug A. Patterns in current perioperative practice: survey of colorectal surgeons in five northern European countries. Br Med J. 2005 06/18/;330(7505):1420-1.

Lawson RM, Doshi MK, Barton JR, Cobden I. The effect of unselected post-operative nutritional supplementation on nutritional status and clinical outcome of orthopaedic patients. Clin Nutr. 2003 Feb 1;22(1):39-46.

Levy BF, Scott MJ, Fawcett W, Fry C, Rockall TA. Randomized clinical trial of epidural, spinal or patient-controlled analgesia for patients undergoing laparoscopic colorectal surgery. Br J Surg. [Randomized Controlled Trial]. 2011 Aug;98(8):1068-78.

Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. Br Med J. 2001 10/06/;323(7316):773-6.

Lin H, Prather C, Fisher R, Meyer J, Summers R, Pimentel M, Mccallum R, Akkermans LM, Loening-Baucke V, Transit ATFCoG. Measurement of gastrointestinal transit. Dig Dis Sci. 2005 Jun 1;50(6):989-1004.

Liu C-L, Fan S-T, Lo C-M, Wong Y, Ng IO-L, Lam C-M, Poon RT-P, Wong J. Abdominal drainage after hepatic resection is contraindicated in patients with chronic liver diseases. Ann Surg. 2004 Feb 1;239(2):194-201.

Liu SS, Carpenter RL, Mackey DC, Thirlby RC, Rupp SM, Shine TS, Feinglass NG, Metzger PP, Fulmer JT, Smith SL. Effects of perioperative analgesic technique on rate of recovery after colon surgery. Anesthesiology. 1995 10;83(4):757-65.

Ljungqvist O, Soreide E. Preoperative fasting. Br J Surg. 2003 Apr;90(4):400-6.

Lobo DN, Bostock KA, Bush D, Macdonald IA, Perkins AC, Neal KR, Rowlands BJ, Allison SP. Reproducibility and normal ranges for gastric emptying in normal volunteers using a test meal designed for post-operative patients. Nucl Med Commun. 2002 Jan 1;23(1):97-101.

Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. Lancet. 2002 05/25/;359(9320):1812-8.

Lobo DN, Macafee DA, Allison SP. How perioperative fluid balance influences postoperative outcomes. Best Pract Res Clin Anaesthesiol. 2006 Sep 1;20(3):439-55.

Luckey A, Livingston E, Taché Y. Mechanisms and treatment of postoperative ileus. Arch Surg. 2003 Feb 1;138(2):206-14.

Ludwig K, Enker WE, Delaney CP, Wolff BG, Du W, Fort JG, Cherubini M, Cucinotta J, Techner L. Gastrointestinal tract recovery in patients undergoing bowel resection: results of a randomized trial of alvimopan and placebo with a standardized accelerated postoperative care pathway. Arch Surg. 2008 Nov 1;143(11):1098-105.

MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, Mitchell CJ. Oral dietary supplements in pre- and postoperative surgical patients: a prospective and randomized clinical trial. Nutrition. 2000 Sep 1;16(9):723-8.

MacKay G, Ihedioha U, McConnachie A, Serpell M, Molloy RG, O'Dwyer PJ. Laparoscopic colonic resection in fast-track patients does not enhance short-term recovery after elective surgery. Colorectal Dis. 2007 May 1;9(4):368-72.

Maessen J, Dejong C, Kessels AG, von Meyenfeldt MF, Group obotERASE. Length of Stay: An Inappropriate Readout of the Success of Enhanced Recovery Programs. World J Surg. 2008 Jun 1;32(6):971-5.

Maessen J, Dejong CH, Hausel J, Nygren J, Lassen K, Andersen J, Kessels AG, Revhaug A, Kehlet H, Ljungqvist O, Fearon KC, von Meyenfeldt MF. A protocol is not enough to implement an enhanced recovery programme for colorectal resection. Br J Surg. 2007 Feb;94(2):224-31.

Maltby JR, Pytka S, Watson NC, Cowan RA, Fick GH. Drinking 300 mL of clear fluid two hours before surgery has no effect on gastric fluid volume and pH in fasting and non-fasting obese patients. Can J Anaesth. 2004 Feb 1;51(2):111-5.

Manku K, Bacchetti P, Leung JM. Prognostic significance of postoperative in-hospital complications in elderly patients. I. Long-term survival. Anesth Analg. 2003 Feb;96(2):583-9, table of contents.

Manton KG, Vaupel JW. Survival after the age of 80 in the United States, Sweden, France, England, and Japan. N Engl J Med. 1995 Nov 2;333(18):1232-5.

Marciani L, Gowland PA, Spiller RC, Manoj P, Moore RJ, Young P, Fillery-Travis AJ. Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI. Am J Physiol Gastrointest Liver Physiol. 2001 Jun 1;280(6):G1227-33.

Marret E, Remy C, Bonnet F, Group PPF. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. Br J Surg. 2007 Jun 1;94(6):665-73.

McMahon M, Marsh H, Rizza R. Comparison of the pattern of postprandial carbohydrate metabolism after ingestion of a glucose drink or a mixed meal. J Clin Endocrinol Metab. 1989 Mar 1;68(3):647-53.

Memon MA, Beckingham IJ. Surgical resection of colorectal liver metastases. Colorectal Dis. 2001 Nov 1;3(6):361-73.

Miedema BW, Johnson JO. Methods for decreasing postoperative gut dysmotility. Lancet Oncol. 2003 Jun 1;4(6):365-72.

Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology. 2002 Mar 1;96(3):725-41.

Moller C, Kehlet H, Friland SG, Schouenborg LO, Lund C, Ottesen B. Fast track hysterectomy. Eur J Obstet Gynecol Reprod Biol. 2001 09;98(1):18-22.

Montejo JC, Zarazaga A, López-Martínez J, Urrútia G, Roqué M, Blesa AL, Celaya S, Conejero R, Galbán C, García de Lorenzo A, Grau T, Mesejo A, Ortiz-Leyba C, Planas M, Ordóñez J, Jiménez FJ, Units SSoICMaC. Immunonutrition in the intensive care unit. A systematic review and consensus statement. Clin Nutr. 2003 Jul;22(3):221-33.

Moore JG, Datz FL, Christian PE, Greenberg E, Alazraki N. Effect of body posture on radionuclide measurements of gastric emptying. Dig Dis Sci. 1988 Dec 1;33(12):1592-5.

Murphy MA, Richards T, Atkinson C, Perkins J, Hands LJ. Fast track open aortic surgery: reduced post operative stay with a goal directed pathway. Eur J Vasc Endovasc Surg. 2007 Sep 1;34(3):274-8.

Murphy PM, Modi P, Rahamim J, Wheatley T, Lewis SJ. An investigation into the current peri-operative nutritional management of oesophageal carcinoma patients in major carcinoma centres in England. Ann R Coll Surg Engl. 2006 Jul;88(4):358-62.

National Institute for Health and Clinical Excellence. Nutritional support in adults: oral supplements, enteral tube feeding and parenteral nutrition.2006; (CG55): Available from: http://www.nice.org.uk/nicemedia/pdf/cg032fullguideline.pdf.

Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. Cochrane Database Syst Rev. 2007 Jan 1(3):CD004929.

Nikfarjam M, Shereef S, Kimchi ET, Gusani NJ, Jiang Y, Avella DM, Mahraj RP, Staveley-O'Carroll KF. Survival outcomes of patients with colorectal liver metastases following hepatic resection or ablation in the era of effective chemotherapy. Ann Surg Oncol. 2009 Jul 1;16(7):1860-7.

Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. Anesthesiology. 2005 07;103(1):25-32.

Noblett SE, Watson DS, Huong H, Davison B, Hainsworth PJ, Horgan AF. Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. Colorectal Dis. 2006 09;8(7):563-9.

Nygren J. The metabolic effects of fasting and surgery. Best Pract Res Clin Anaesthesiol. 2006 Sep 1;20(3):429-38.

Nygren J, Hausel J, Kehlet H, Revhaug A, Lassen K, Dejong C, Andersen J, von Meyenfeldt M, Ljungqvist O, Fearon KC. A comparison in five European Centres of case mix, clinical management and outcomes following either conventional or fast-track perioperative care in colorectal surgery. Clin Nutr. 2005 Jun;24(3):455-61.

Nygren J, Soop M, Thorell A, Efendic S, Nair KS, Ljungqvist O. Preoperative oral carbohydrate administration reduces postoperative insulin resistance. Clin Nutr. 1998 Apr 1;17(2):65-71.

Nygren J, Thorell A, Jacobsson H, Larsson S, Schnell PO, Hylén L, Ljungqvist O. Preoperative gastric emptying. Effects of anxiety and oral carbohydrate administration. Ann Surg. 1995 Dec 1;222(6):728-34.

Nygren J, Thorell A, Ljungqvist O. Preoperative oral carbohydrate nutrition: an update. Curr Opin Clin Nutr Metab Care. 2001 Jul 1;4(4):255-9.

O'Dwyer PJ, McGregor JR, McDermott EW, Murphy JJ, O'Higgins NJ. Patient recovery following cholecystectomy through a 6 cm or 15 cm transverse subcostal incision: a prospective randomized clinical trial. Postgrad Med J. 1992 10;68(804):817-9.

Older P, Hall A. Clinical review: how to identify high-risk surgical patients. Crit Care. [Review]. 2004 Oct;8(5):369-72.

Older P, Smith R, Hall A, French C. Preoperative cardiopulmonary risk assessment by cardiopulmonary exercise testing. Crit Care Resusc. 2000 Sep;2(3):198-208.

Ong ES, Alassas M, Dunn KB, Rajput A. Colorectal cancer surgery in the elderly: acceptable morbidity? Am J Surg. 2008 Mar;195(3):344-8; discussion 8.

Ottesen M, Sørensen M, Rasmussen Y, Smidt-Jensen S, Kehlet H, Ottesen B. Fast track vaginal surgery. Acta Obstet Gynecol Scand. 2002 Feb 1;81(2):138-46.

Parnaby C, Macdonald A, Jenkins J. Sham feed or sham? A meta-analysis of randomized clinical trials assessing the effect of gum chewing on gut function after elective colorectal surgery. Int J Colorectal Dis. 2009 Jan 17.

Pessaux P, Regimbeau J, Dondéro F, Plasse M, Mantz J, Belghiti J. Randomized clinical trial evaluating the need for routine nasogastric decompression after elective hepatic resection. Br J Surg. 2007 Mar 1;94(3):297-303.

Petrowsky H, Demartines N, Rousson V, Clavien P. Evidence-based Value of Prophylactic Drainage in Gastrointestinal Surgery. Ann Surg. 2004 Dec 1;240(6):1074-85.

Petrowsky H, McCormack L, Trujillo M, Selzner M, Jochum W, Clavien PA. A prospective, randomized, controlled trial comparing intermittent portal triad clamping versus ischemic preconditioning with continuous clamping for major liver resection. Ann Surg. 2006 Dec 1;244(6):921-8; discussion 8-30.

Platell C, Barwood N, Makin G. Randomized clinical trial of bowel preparation with a single phosphate enema or polyethylene glycol before elective colorectal surgery. Br J Surg. 2006 04;93(4):427-33.

Podore PC, Throop EB. Infrarenal aortic surgery with a 3-day hospital stay: A report on success with a clinical pathway. J Vasc Surg. 1999 May 1;29(5):787-92.

Polanczyk CA, Marcantonio E, Goldman L, Rohde LE, Orav J, Mangione CM, Lee TH. Impact of age on perioperative complications and length of stay in patients undergoing noncardiac surgery. Ann Intern Med. 2001 Apr 17;134(8):637-43.

Preston T, McMillan DC. Rapid sample throughput for biomedical stable isotope tracer studies. Biomed Environ Mass Spectrom. 1988 Oct 1;16(1-12):229-35.

Prytherch DR, Whiteley MS, Higgins B, Weaver PC, Prout WG, Powell SJ. POSSUM and Portsmouth POSSUM for predicting mortality. Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. Br J Surg. 1998 Sep;85(9):1217-20.

Rahbari NN, Zimmermann JB, Schmidt T, Koch M, Weigand MA, Weitz J. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. Br J Surg. 2009 Apr 1;96(4):331-41.

Ram E, Sherman Y, Weil R, Vishne T, Kravarusic D, Dreznik Z. Is mechanical bowel preparation mandatory for elective colon surgery? A prospective randomized study. ArchSurg. 2005 03;140(3):285-8.

Rana SK, Bray J, Menzies-Gow N, Jameson J, Payne James JJ, Frost P, Silk DB. Short term benefits of post-operative oral dietary supplements in surgical patients. Clin Nutr. 1992 Dec 1;11(6):337-44.

Reissman P, Teoh TA, Cohen SM, Weiss EG, Nogueras JJ, Wexner SD. Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. Ann Surg. 1995 07;222(1):73-7.

Rivière PJ, Pascaud X, Chevalier E, Le Gallou B, Junien JL. Fedotozine reverses ileus induced by surgery or peritonitis: action at peripheral kappa-opioid receptors. Gastroenterology. 1993 Mar 1;104(3):724-31.

Roth E. Nonnutritive effects of glutamine. J Nutr. 2008 Oct 1;138(10):2025S-31S.

Rothman DL, Magnusson I, Katz LD, Shulman RG, Shulman GI. Quantitation of hepatic glycogenolysis and gluconeogenesis in fasting humans with 13C NMR. Science. 1991 10/25/;254(5031):573-6.

Salerno G, Daniels IR, Brown G, Heald RJ, Moran BJ. Magnetic resonance imaging pelvimetry in 186 patients with rectal cancer confirms an overlap in pelvic size between males and females. Colorectal Dis. 2006 Nov;8(9):772-6.

Sanaka M, Yamamoto T, Kuyama Y. Retention, fixation, and loss of the [13C] label: a review for the understanding of gastric emptying breath tests. Dig Dis Sci. 2008 Jul 1;53(7):1747-56.

Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. Lancet. 1996 02/03/;347(8997):289-92.

Schoeller. A Simplified Technique for Collecting Breath CO, for Isotope Ratio Mass Spectrometry. 2005 Feb 04:1-3.

Schoetz DJ, Bockler M, Rosenblatt MS, Malhotra S, Roberts PL, Murray JJ, Coller JA, Rusin LC. "Ideal" length of stay after colectomy: whose ideal? Dis Colon Rectum. 1997 Jul 1;40(7):806-10.

Schricker T, Lattermann R, Fiset P, Wykes L, Carli F. Integrated analysis of protein and glucose metabolism during surgery: effects of anesthesia. J Appl Physiol. 2001 Dec 1;91(6):2523-30.

Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. Ann Surg. 2006 Mar 1;243(3):373-9.

Schwizer W, Fraser R, Borovicka J, Crelier G, Boesiger P, Fried M. Measurement of gastric emptying and gastric motility by magnetic resonance imaging (MRI). Dig Dis Sci. 1994 Dec 1;39(12 Suppl):101S-3S.

Schwizer W, Maecke H, Fried M. Measurement of gastric emptying by magnetic resonance imaging in humans. Gastroenterology. 1992 Aug 1;103(2):369-76.

Scott EM, Buckland R. A systematic review of intraoperative warming to prevent postoperative complications. AORN J. 2006 May 1;83(5):1090-104, 107-13.

Senagore AJ, Delaney CP, Mekhail N, Dugan A, Fazio VW. Randomized clinical trial comparing epidural anaesthesia and patient-controlled analgesia after laparoscopic segmental colectomy. Br J Surg. 2003 10;90(10):1195-9.

Seymour DG, Pringle R. Elderly patients in a general surgical unit: do they block beds? Br Med J. 1982 Jun 26;284(6333):1921-3.

Shaw JH, Wolfe RR. Energy and protein metabolism in sepsis and trauma. Aust N Z J Surg. 1987 Jan 1;57(1):41-7.

Shepperd S, Parkes J, McClaren J, Phillips C. Discharge planning from hospital to home. Cochrane database of systematic reviews (Online). [Meta-Analysis]. 2004(1):CD000313.

Siegel JA, Urbain JL, Adler LP, Charkes ND, Maurer AH, Krevsky B, Knight LC, Fisher RS, Malmud LS. Biphasic nature of gastric emptying. Gut. 1988 Jan 1;29(1):85-9.

Slater C, Preston T, Weaver LT. Comparison of accuracy and precision of heart rate calibration methods to estimate total carbon dioxide production during 13C-breath tests. Eur J Clin Nutr. 2006 Jan;60(1):69-76.

Slim K, Vicaut E, Panis Y, Chipponi J. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. Br J Surg. 2004 Sep 20;91(9):1125-30.

Smedley F, Bowling T, James M, Stokes E, Goodger C, O'Connor O, Oldale C, Jones P, Silk D. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. Br J Surg. 2004 08;91(8):983-90.

Smith AF, Pittaway AJ. Premedication for anxiety in adult day surgery. Cochrane Database Syst Rev. 2003 Jan 1(1):CD002192.

Smith JJ, Lee J, Burke C, Contractor KB, Dawson PM. Major colorectal cancer resection should not be denied to the elderly. Eur J Surg Oncol. 2002 Sep 1;28(6):661-6.

Soop M, Carlson GL, Hopkinson J, Clarke S, Thorell A, Nygren J, Ljungqvist O. Randomized clinical trial of the effects of immediate enteral nutrition on metabolic responses to major colorectal surgery in an enhanced recovery protocol. Br J Surg. 2004 Sep;91(9):1138-45.

Soop M, Nygren J, Myrenfors P, Thorell A, Ljungqvist O. Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. Am J Physiol Endocrinol Metab. 2001 04;280(4):E576-E83.

Soop M, Nygren J, Thorell A, Weidenhielm L, Lundberg M, Hammarqvist F, Ljungqvist O. Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery. Clin Nutr. 2004 Aug 1;23(4):733-41.

Søreide E, Ljungqvist O. Modern preoperative fasting guidelines: a summary of the present recommendations and remaining questions. Best Pract Res Clin Anaesthesiol. 2006 Sep 1;20(3):483-91.

Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. Cochrane Database Syst Rev. [Meta-Analysis]. 2011(2):CD007635.

Starnes HF, Warren RS, Jeevanandam M, Gabrilove JL, Larchian W, Oettgen HF, Brennan MF. Tumor necrosis factor and the acute metabolic response to tissue injury in man. J Clin Invest. 1988 Oct 1;82(4):1321-5.

Stewart BT, Woods RJ, Collopy BT, Fink RJ, Mackay JR, Keck JO. Early feeding after elective open colorectal resections: a prospective randomized trial. Aust N Z J Surg. 1998 Feb 1;68(2):125-8.

Studley HO. Percentage of weight loss with physical impairment: a basic indicator of surgical risk in patients with chronic peptic ulcer. JAMA. 1936 07;106(4):458-60.

Svanfeldt M, Thorell A, Hausel J, Soop M, Nygren J, Ljungqvist O. Effect of "preoperative" oral carbohydrate treatment on insulin action--a randomised cross-over unblinded study in healthy subjects. Clin Nutr. 2005 10;24(5):815-21.

Svanfeldt M, Thorell A, Hausel J, Soop M, Rooyackers O, Nygren J, Ljungqvist O. Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics. Br J Surg. 2007 Nov 1;94(11):1342-50.

Tambyraja AL, Sengupta F, MacGregor AB, Bartolo DC, Fearon KC. Patterns and clinical outcomes associated with routine intravenous sodium and fluid administration after colorectal resection. World J Surg. 2004 10;28(10):1046-51.

Taylor IL, Byrne WJ, Christie DL, Ament ME, Walsh JH. Effect of individual l-amino acids on gastric acid secretion and serum gastrin and pancreatic polypeptide release in humans. Gastroenterology. 1982 Jul 1;83(1 Pt 2):273-8.

Tekkis PP, Poloniecki JD, Thompson MR, Stamatakis JD. Operative mortality in colorectal cancer: prospective national study. Br Med J. 2003 Nov 22;327(7425):1196-201.

Thorell A, Efendic S, Gutniak M, Häggmark T, Ljungqvist O. Development of postoperative insulin resistance is associated with the magnitude of operation. Eur J Surg. 1993 Jan 1;159(11-12):593-9.

Thorell A, Nygren J, Hirshman MF, Hayashi T, Nair KS, Horton ES, Goodyear LJ, Ljungqvist O. Surgery-induced insulin resistance in human patients: relation to glucose transport and utilization. Am J Physiol. 1999 Apr 1;276(4 Pt 1):E754-61.

Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. Curr Opin Clin Nutr Metab Care. 1999 Jan 1;2(1):69-78.

Tjandra JJ, Chan MKY. Systematic review on the short-term outcome of laparoscopic resection for colon and rectosigmoid cancer. Colorectal Dis. 2006 Jun 1;8(5):375-88.

Tjandra JJ, Tagkalidis P. Carbohydrate-electrolyte (E-Lyte) solution enhances bowel preparation with oral fleet phospho-soda. Dis Colon Rectum. 2004 07;47(7):1181-6.

Traut U, Brügger L, Kunz R, Pauli-Magnus C, Haug K, Bucher HC, Koller MT. Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults. Cochrane Database Syst Rev. 2008 Jan 1(1):CD004930.

Uchida I, Asoh T, Shirasaka C, Tsuji H. Effect of epidural analgesia on postoperative insulin resistance as evaluated by insulin clamp technique. Br J Surg. 1988 Jun 1;75(6):557-62.

van Doorslaer EK, van Vliet RC. "A built bed is a filled bed?" An empirical re-examination. Soc Sci Med. 1989 Jan 1;28(2):155-64.

van Stijn MFM, Boelens PG, Richir MC, Ligthart-Melis GC, Twisk JWR, Diks J, Houdijk APJ, van Leeuwen PAM. Antioxidant-enriched enteral nutrition and immuno-inflammatory response after major gastrointestinal tract surgery. The British journal of nutrition. 2010 Mar;103(3):314-8.

Varadhan KK, Neal KR, Dejong CHC, Fearon KCH, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: A meta-analysis of randomized controlled trials. Clin Nutr. 2010 Jan 27.

Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Påhlman L, Cuesta MA, Msika S, Morino M, Lacy AM, (COLOR) CcLoORSG. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol. 2005 Jul 1;6(7):477-84.

Walldén J, Thörn S, Lövqvist Å, Wattwil L, Wattwil M. The effect of anesthetic technique on early postoperative gastric emptying: comparison of propofol-remifentanil and opioid-free sevoflurane anesthesia. J Anesth. 2006 Oct 27;20(4):261-7.

Warschkow R, Tarantino I, Torzewski M, Näf F, Lange J, Steffen T. Diagnostic accuracy of C-reactive protein and white blood cell counts in the early detection of inflammatory complications after open resection of colorectal cancer: a retrospective study of 1,187 patients. Int J Colorectal Dis. 2011 Nov;26(11):1405-13.

Wattwil M, Thörn S-E, Lövqvist A, Wattwil L, Klockhoff H, Larsson L-G, Näslund I. Perioperative gastric emptying is not a predictor of early postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. Anesth Analg. 2002 Aug 1;95(2):476-9, table of contents.

Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, Jauch KW, Kemen M, Hiesmayr JM, Horbach T, Kuse ER, Vestweber KH. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clin Nutr. 2006 Apr;25(2):224-44.

Wille-Jorgensen P, Guenaga KF, Castro AA, Matos D. Clinical value of preoperative mechanical bowel cleansing in elective colorectal surgery: a systematic review. Dis Colon Rectum. 2003 Aug;46(8):1013-20.

Wilmore DW. From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. Ann Surg. 2002 Nov 1;236(5):643-8.

Wind J, Polle SW, Fung Kon Jin PH, Dejong CH, von Meyenfeldt MF, Ubbink DT, Gouma DJ, Bemelman WA. Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg. 2006 Jul;93(7):800-9.

Wong PF, Kumar S, Bohra A, Whetter D, Leaper DJ. Randomized clinical trial of perioperative systemic warming in major elective abdominal surgery. Br J Surg. 2007 Apr 1;94(4):421-6.

Woods DM, Macpherson R. Australian and New Zealand guidelines for preoperative fasting. Anaesth Intensive Care. 2007 Aug 1;35(4):622-3.

World Health Organisation. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000 Jan 1;894:i-xii, 1-253.

Yuill KA, Richardson RA, Davidson HI, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively--a randomised clinical trial. Clin Nutr. 2005 Feb 1;24(1):32-7.

Zhang K, Pi-Sunyer FX, Boozer CN. Improving energy expenditure estimation for physical activity. Med Sci Sports Exerc. 2004 May 1;36(5):883-9.

Zingg U, Miskovic D, Pasternak I, Meyer P, Hamel CT, Metzger U. Effect of bisacodyl on postoperative bowel motility in elective colorectal surgery: a prospective, randomized trial. Int J Colorectal Dis. 2008 Dec 1;23(12):1175-83.

Zutshi M, Delaney CP, Senagore AJ, Fazio VW. Shorter hospital stay associated with fastrack postoperative care pathways and laparoscopic intestinal resection are not associated with increased physical activity. Colorectal Dis. 2004 Nov 1;6(6):477-80.

Original article

doi:10.1111/j.1463-1318.2008.01499.x

# Preoperative conditioning with oral carbohydrate loading and oral nutritional supplements can be combined with mechanical bowel preparation prior to elective colorectal resection

**P. O. Hendry*, A. Balfour†, M. A. Potter†, B. J. Mander†, D. C. C. Bartolo†, D. N. Anderson† and K. C. H. Fearon***

*Department of Clinical and Surgical Sciences, Royal Infirmary of Edinburgh and †Colorectal Unit, Western General Hospital, Edinburgh, UK

Received 4 October 2007; accepted 24 December 2007

## Abstract

**Objective** Preoperative conditioning with oral fluid and carbohydrate (CHO) loading allows the patient to undergo surgery in the fed state and is associated with reduced postoperative insulin resistance. Further benefit may accrue from oral nutritional supplements (ONS) to counteract the fasting associated with mechanical bowel preparation (MBP). In this study we assess the ability to prescribe, dispense and have patients comply with a protocol combining preoperative ONS and CHO/fluid loading during MBP.

**Method** One hundred and forty-seven patients undergoing elective left colonic or rectal resection were recruited to an Enhanced Recovery after Surgery (ERAS) programme. All patients were prescribed MBP (2 sachets Picolax). On the daytime prior to surgery, eligible patients were prescribed 2 × 200 ml of ONS (Fortijuice®, Nutricia) and in the evening 800 ml oral CHO/fluid loading (Preop®, Nutricia,). Patients were prescribed a further 400 ml of oral/CHO/fluid on the morning of surgery 2 h prior to induction of anaesthesia. Protocol compliance was audited prospectively.

**Results** One hundred and forty-seven patients received MBP. Twenty-three patients were ineligible for oral CHO/fluid loading [diabetes ($n$ = 22), allergy to lemon flavoured drinks ($n$ = 1)]. Fourteen patients did not receive the preoperative CHO drinks due to failure to prescribe ($n$ = 8) or dispense ($n$ = 6). One hundred and ten patients were dispensed the combined ONS and CHO/fluid loading regimen, compliance rates were 83% with ONS, 80% with CHO/fluid loading and 74% with both.

**Conclusion** Approximately 74% of patients undergoing MBP can comply with preoperative conditioning with ONS and CHO/fluid loading. Prescription and dispensing requires close attention to detail.

**Keywords** Enhanced recovery after surgery, preoperative conditioning, carbohydrate loading, mechanical bowel preparation, investigation

## Introduction

Preoperative oral carbohydrate (CHO) and fluid loading is a common component of enhanced recovery after surgery (ERAS) programmes and is thought to maintain postoperative nutritional status by reducing postoperative insulin resistance [1]. Preoperative fluid and CHO loading has been shown to reduce postoperative hyperglycaemia and nitrogen loss and to aid postoperative recovery [2]. Within the context of traditional perioperative care, early postoperative oral or enteral nutritional support has been shown to reduce both infectious complications and length of stay [3]. Use of preoperative CHO loading to reduce postoperative insulin resistance may further optimize the benefits of such early postoperative feeding.

Traditional periods of perioperative fasting beyond that recommended by National Anaesthesia Societies are still prevalent [4] and are often prolonged due to concomitant use of mechanical bowel preparation (MBP). Prolonged fasting decreases the capacity to cope with the surgical stress response, increases postoperative insulin resistance and may affect adversely length of stay

*Correspondence to*: Mr Paul O. Hendry, University Department of Surgery, Clinical and Surgical Sciences (Surgery), Royal Infirmary, 51 Little France, Crescent, Edinburgh EH16 4SA, UK.
E-mail: paul.hendry@ed.ac.uk

[5]. Such fasting may also compromise further the fluid and electrolyte balance of patients receiving MBP [6]. The use of MBP in colorectal surgery is common [7]. This is often due to surgical preference [8] despite recent evidence that questions the benefit of MBP [9]. Whilst preoperative fasting for 6 h is required for solids, clear fluids should be encouraged up to 2 h prior to surgery [10]. Specially designed polymeric CHO beverages can also be administered up to 2 h prior to surgery as they are safe and will empty from the stomach within 120 min [11] and as glucose absorption occurs rapidly in the upper gastrointestinal tract and is unaffected by administered prokinetc agents [12] it is unlikely to be affected by MBP.

The aim of this study was to demonstrate that patients can comply with routine preoperative conditioning with an oral CHO solution in conjunction with MBP prior to elective left colonic or rectal resection.

## Method

This study was conducted in the colorectal unit at the Western General Hospital in Edinburgh, UK. Ethical approval was obtained from Lothian Research Ethics committee and written consent obtained from each patient after verbal and written information had been provided in a clinic visit prior to admission. Patients undergoing elective left colonic or rectal resection for benign or malignant disease were recruited and were prescribed preoperative MBP (2 sachets of Picolax® (Picolax®, Ferring Pharmaceuticals (UK), Langley, UK)). Patients followed an ERAS protocol as previously published [13]. As part of the ERAS protocol the ERAS research nurse either provided the drinks/instructions at the preadmission clinic or for in-patients requested the surgical house officer to prescribe the following regimen on the patients drug chart: 200 ml of an oral nutritional supplement (ONS: Fortijuice®, Nutricia Clinical Care, Trowbridge, UK) prior to the first sachet of bowel preparation and another 200 ml of ONS prior the second sachet of bowel preparation. Nondiabetic patients were prescribed oral CHO/fluid as 400–800 ml of a 12.5% clear beverage (Preop®, Nutricia Clinical Care, Trowbridge, UK) at 8 p.m. the evening before surgery and a further 400 ml 2–3 h before surgery (Fig. 1). Compliance with the protocol was audited prospectively.

## Results

One hundred and forty seven patients underwent elective left colonic ($n$ = 42) or rectal resection ($n$ = 105) and received MBP. There were 70 males and 77 females. Mean (SD) age was 64 (14.2). Twenty-two were diabetic and were not eligible to receive preoperative CHO/fluid loading. One patient did not receive the CHO loading due to an allergy to lemon flavoured drinks. There were 124 patients eligible to undertake the protocol. The protocol failed in 14 patients (eight regimen not prescribed by the medical staff, six regimen not dispensed by the nursing staff). Of the patients that were eligible to undertake the protocol, 99 (80%) completed the prescribed volume of CHO/fluid loading with no adverse effects. Eleven patients did not complete the CHO drinks, seven patients did not tolerate them, two refused to try them, one patient vomited and in one case the reason was not recorded. One hundred and three (83%) completed the full prescribed volume of ONS and 92 patients completed the combined regimen of ONS and CHO drinks. In summary, 92 (74%) of 124 patients that were eligible tolerated the drinks and completed the regimen (Fig. 2).

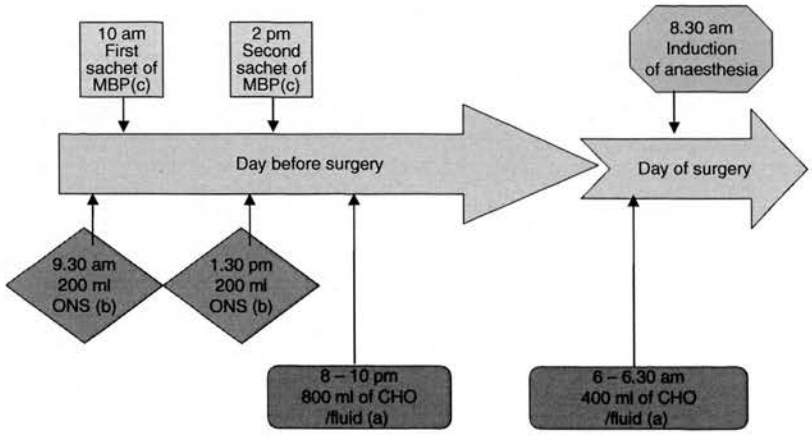



**Figure 1** Preoperative protocol. (a) CHO/fluid: carbohydrate and fluid loading (Preop®, Nutricia). (b) ONS: oral nutritional supplement (Fortijuice®, Nutricia). (c) MBP: mechanical bowel preparation (Picolax).

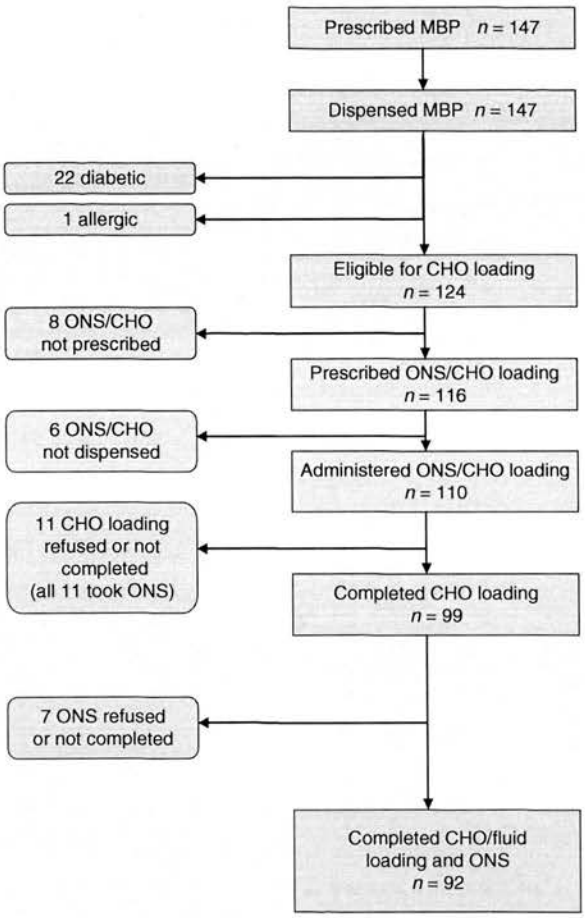



**Figure 2** Consort diagram. CHO/fluid: carbohydrate and fluid loading (Preop®, Nutricia). ONS: oral nutritional supplement (Fortisip®, Nutricia).

## Discussion

In this study, we have shown that 84% of patients can tolerate preoperative oral fluid/CHO loading and ONS in conjunction with MBP prior to elective left colonic or rectal resection. A previous study by Tjandra and Tagkalidis [14] examined oral CHO/electrolyte replacement in conjunction with MBP prior to colonoscopy and demonstrated a similar level of tolerance. Taken together, these findings suggest it is feasible to prescribe simultaneous MBP and CHO/fluid loading and that patients will comply well with both regimens. Interestingly, a recent study by Noblett *et al.* [15] used preoperative CHO/fluid loading and showed a high level of compliance and earlier functional recovery following colorectal surgery but it was not clear whether patients had received concomitant MBP.

The protocol used in our study was designed to account for the fact that during MBP patients cannot eat solid food and require extra oral fluids to counteract dehydration. Recent evidence from Ljungqvist *et al.* (the group that originally demonstrated the benefits of preoperative oral CHO/fluid loading) has shown that 400 ml oral CHO/fluid loading 2 h prior to induction of anaesthesia is sufficient to reduce postoperative insulin resistance if the patients take normal food until 10 p.m. on the previous day. The 800 ml oral CHO/fluid loading the evening before surgery does not add to the improved metabolic status and decreased postoperative insulin resistance [16]. In the light of these recent findings it might be possible to omit the CHO/fluid loading at 8–10 pm the night before surgery and replace this with further ONS and clear fluids.

In the present study approximately 15% of all patients were 'ineligible' for oral CHO loading due to the presence of diabetes. Diabetes, is, however, only a relative contra-indication and CHO loading in diabetic patients is currently the subject of at least one randomized study (O. Ljungqvist, Ersta Hospital, Stockholm, Sweden, personal communication). A second issue raised by the present study is that of protocol failure. Clearly the present regimen represents a more complex form of preoperative preparation than simply starving the patient for 12 h. Protocol failure (11%) was due either to failure to prescribe the regimen or failure to dispense the regimen. This occurred almost exclusively in those patients who received MBP as inpatients. Clearly similar issues are more easily avoided in patients prepared at home and admitted on the same day as surgery.

The haemodynamic and metabolic benefits of preoperative CHO and fluid loading are clear and should not be denied to patients receiving MBP. From the present study it is apparent that with a clearly defined protocol patients undergoing MBP are well able to complete a regimen of CHO/fluid loading combined with ONS.

## Acknowledgements

During the period of this study the ERAS group was supported by an unrestricted grant from Nutricia healthcare.

## Conflicts of interest

None declared.

## References

1 Nygren J, Soop M, Thorell A *et al.* Preoperative oral carbohydrate administration reduces postoperative insulin resistance. *Clin Nutr* 1998; **17**: 65–71.

2 Yuill KA, Richardson RA, Davidson HI, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing

fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively – a randomised clinical trial. *Clin Nutr* 2005; **24:** 32–7.

3 Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. *BMJ* 2001; **323:** 773–6.

4 Hannemann P, Lassen K, Hausel J *et al.* Patterns in current anaesthesiological peri-operative practice for colonic resections: a survey in five northern-European countries. *Acta Anaesthesiol Scand* 2006; **50:** 1152–60.

5 Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. *Curr Opin Clin Nutr Metab Care* 1999; **2:** 69–78.

6 Rothman DL, Magnusson I, Katz LD, Shulman RG, Shulman GI. Quantitation of hepatic glycogenolysis and gluconeogenesis in fasting humans with 13C NMR. *Science* 1991; **254:** 573–6.

7 Nygren J, Hausel J, Kehlet H *et al.* A comparison in five European centres of case mix, clinical management and outcomes following either conventional or fast-track perioperative care in colorectal surgery. *Clin Nutr* 2005; **24:** 455–61.

8 Lassen K, Hannemann P, Ljungqvist O *et al.* Patterns in current perioperative practice: survey of colorectal surgeons in five northern European countries. *BMJ* 2005; **330:** 1420–1.

9 Bucher P, Mermillod B, Gervaz P, Morel P. Mechanical bowel preparation for elective colorectal surgery: a meta-analysis. *Arch Surg* 2004; **139:** 1359–64.

10 Ljungqvist O, Soreide E. Preoperative fasting. *Br J Surg* 2003; **90:** 400–6.

11 Nygren J, Thorell A, Jacobsson H *et al.* Preoperative gastric emptying. Effects of anxiety and oral carbohydrate administration. *Ann Surg* 1995; **222:** 728–34.

12 Brunetto AL, Pearson AD, Gibson R *et al.* The effect of pharmacological modification of gastric emptying and mouth-to-caecum transit time on the absorption of sugar probe marker molecules of intestinal permeability in normal man. *Eur J Clin Invest* 1990; **20:** 279–84.

13 Fearon KC, Ljungqvist O, von Meyenfeldt MF *et al.* Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr* 2005; **24:** 466–77.

14 Tjandra JJ, Tagkalidis P. Carbohydrate-electrolyte (E-Lyte) solution enhances bowel preparation with oral fleet phospho-soda. *Dis Colon Rectum* 2004; **47:** 1181–6.

15 Noblett SE, Watson DS, Huong H *et al.* Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. *Colorectal Dis* 2006; **8:** 563–9.

16 Svanfeldt M, Thorell A, Hausel J *et al.* Effect of "preoperative" oral carbohydrate treatment on insulin action – a randomised cross-over unblinded study in healthy subjects. *Clin Nutr* 2005; **24:** 815–21.

Original article

# Initial experience with a multimodal enhanced recovery programme in patients undergoing liver resection

**R. M. van Dam[1], P. O. Hendry[3], M. M. E. Coolsen[1], M. H. A. Bemelmans[1], K. Lassen[4,5], A. Revhaug[4,5], K. C. H. Fearon[3], O. J. Garden[3] and C. H. C. Dejong[1,2], on behalf of the Enhanced Recovery After Surgery (ERAS) Group**

[1]Department of Surgery, Maastricht University Medical Centre and [2]Nutrition and Toxicology Research Institute, Maastricht University, Maastricht, The Netherlands, [3]Department of Surgery, Royal Infirmary, Edinburgh, UK, and [4]Department of Gastrointestinal Surgery, University Hospital Northern Norway, and [5]Faculty of Medicine, University of Tromsø, Tromsø, Norway

*Correspondence to:* Dr R. M. van Dam, Department of Surgery, Maastricht University Medical Centre, PO Box 5800, 6202 AZ Maastricht, The Netherlands (e-mail: rvdm@surgery.azm.nl)

**Background:** Accelerated recovery from surgery has been achieved when patients are managed within a multimodal Enhanced Recovery After Surgery (ERAS) protocol. This study evaluated the benefit of an ERAS programme for patients undergoing liver resection.

**Methods:** The ERAS protocol of epidural analgesia, early oral intake and early mobilization was studied prospectively in a consecutive series of 61 patients. Outcomes were compared with those in a consecutive series of 100 patients who underwent liver resection before the start of the study. Endpoints were postoperative length of hospital stay, postoperative resumption of oral intake, readmissions, morbidity and mortality.

**Results:** Fifty-six patients (92 per cent) in the ERAS group tolerated fluids within 4 h of surgery and a normal diet on day 1 after surgery. Median hospital stay, including readmissions, was 6·0 days compared with 8·0 days in the control group ($P < 0·001$). There were no significant differences in rates of readmission (13 and 10·0 per cent respectively), morbidity (41 and 31·0 per cent) and mortality (0 and 2·0 per cent) between ERAS and control groups.

**Conclusion:** The ERAS fast-track protocol is safe and effective for patients undergoing liver resection. It allows early oral intake, promotes faster postoperative recovery and reduces hospital stay.

Preliminary results of this study were presented to the 27th Congress of the European Society of Clinical Nutrition and Metabolism, Brussels, Belgium, August 2005, the 7th World Congress of the International Hepato-Pancreatic-Biliary Association, Edinburgh, UK, September 2006, and the Annual Scientific Meeting of the Association of Surgeons of Great Britain and Ireland, Manchester, UK, November 2007

Paper accepted 17 June 2008

Published online 00 00 2008 in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.6227

## Introduction

In the past two decades, the application of multimodal perioperative care protocols, commonly referred to as fast-track or enhanced recovery programmes, has achieved significant improvements in the outcome of a variety of surgical procedures. By targeting factors that delay postoperative recovery (pain, gut dysfunction and immobility), and combining a series of interventions to reduce perioperative stress and organ dysfunction, such programmes have been shown to accelerate postoperative recovery and reduce length of hospital stay. This can be achieved with an unaltered or even reduced rate of postoperative complications[1]. Protocols based on postoperative pain control through continuous mid-thoracic epidural anaesthesia, stimulation of gut motility, early physical reactivation, and limited use of catheters, tubes and drains have resulted in improved convalescence for many surgical procedures, including colonic surgery, open aortic aneurysm repair and oesophageal surgery[2–7]. In the past 5 years, the protocol in elective colonic surgery

The Editors are satisfied that all authors have contributed significantly to this publication

established by the Enhanced Recovery After Surgery (ERAS) Group has led to a reduction in median hospital stay from 9 to 5 days[6].

Within a traditional perioperative care pathway median hospital stay following liver surgery ranges from 8 to 14 days[8–11]. Morbidity is reasonably predictable, with haemorrhagic complications occurring predominantly during surgery or in the early postoperative phase, and biliary complications, intra-abdominal abscess or liver failure in the later postoperative phase[12,13]. It was hypothesized that application of an enhanced recovery programme for patients undergoing liver surgery would result in accelerated recovery and a shorter hospital stay. The main aim of the present study was to test the feasibility, safety and effectiveness of an ERAS protocol in patients undergoing liver surgery in two tertiary referral liver units in Europe.

## Methods

The ERAS liver study was initiated within the collaborative ERAS Group, and conducted in two units that perform high-volume liver surgery. The study was a prospective case series implementation study comparing outcomes with those in a historical control group.

The ERAS patient group comprised a consecutive series of 61 patients admitted to either the liver unit of Maastricht University Medical Center, The Netherlands, between 15 February 2005 and 31 August 2006, or the liver unit of the Royal Infirmary of Edinburgh, UK, where patient recruitment started on 1 February 2006. The control group consisted of a consecutive series of 100 patients who had liver resection in one of the two units between 1 July 2003 and 31 December 2004 (50 consecutive patients from each unit), when a more traditional care pathway was still in use. Patient and outcome data were derived from a prospectively collected database of all liver resections performed since 1 January 2000 in both units. In both groups, patients undergoing elective liver resection for primary or secondary tumours were considered eligible for the study if they had normal underlying liver function. Patients were excluded if they required biliary reconstruction or had emergency surgery.

In both units, the same group of liver surgeons performed the liver resections in the ERAS group as well as in the control group. In Maastricht more fellows with hepatopancreatobiliary training operated in the ERAS group. Bilateral subcostal transverse abdominal incisions were used. The transection plane was determined by intraoperative ultrasonography. To avoid excessive blood loss central venous pressure was reduced to below 5 mmHg during transection using the Cavitron Ultrasonic Surgical Aspirator (CUSA®; Valleylab, Boulder, Colorado, USA) and argon beam coagulation. The portal pedicles supplying and veins draining the sectors to be resected were divided and ligated with a running polypropylene suture. After removal of the liver specimen, the raw surface of the liver remnant was subjected to argon beam coagulation and sealed with TachoSil® (Nycomed, Zurich, Switzerland). In accordance with the protocol, no abdominal drains were placed in the ERAS group and the abdomen was closed with a standard running suture.

Before the introduction of the ERAS programme neither of the institutions had a written, agreed perioperative care pathway. There were no specific measures to avoid prolonged preoperative and postoperative fasting, nasogastric decompression, excessive use of intravenous fluids and systemic opioids, prophylactic abdominal drains and postoperative immobilization. This conventional postoperative care programme emphasized prolonged rest for both the patient and the gastrointestinal tract.

The ERAS multimodal evidence-based recovery programme protocol, which was designed originally for elective colonic surgery, was modified to cover all aspects of elective liver resection[2]. Details of the ERAS liver protocol are given in *Table 1*.

In both groups, data were obtained prospectively during the hospital stay and for 90 days after surgery. Data recorded for each patient included morbidity, defined as complications related to the liver surgery, mortality, readmissions, postoperative hospital stay, use of preoperative chemotherapy, duration of surgical procedure, blood loss, anaesthetic agents used and type of hepatectomy, defined according to the Brisbane 2000 terminology[14]. In the ERAS group, data on location of the epidural catheter, removal of the nasogastric tube if used, and time to resumption of oral intake and mobilization were also noted.

The primary endpoint of the study was total length of hospital stay, defined as the number of nights spent in hospital, including nights after readmission within 30 days after surgery. To facilitate objective assessment of clinical outcome and to prevent discharge too soon, predefined discharge criteria were used in the ERAS group (*Table 2*). Patients were informed about the protocol at a preadmission counselling session, where the importance of early mobilization and early oral intake were explained. Patients were discharged only if they met the discharge criteria and follow-up within 3 days was possible in the outpatient clinic. Patients were given the mobile telephone number of the operating consultant surgeon to allow direct communication and safe deployment of the protocol.

**Table 1** Care plan of patients undergoing liver resection in the Enhanced Recovery After Surgery programme

| |
|---|
| Day before surgery |
| Normal oral nutrition until midnight |
| No preanaesthetic medication |
| Day of surgery |
| Carbohydrate drinks up to 2 h before surgery |
| Mid-thoracic epidural analgesia (local anaesthetic + low-dose opioid) |
| Short-acting i.v. anaesthetic agent |
| No nasogastric drainage; if used, remove immediately after surgery |
| Warm i.v. fluids, and upper and lower body air-warming device |
| Avoidance of excessive i.v. fluids (preoperative and peroperative CVP < 5 mmHg) |
| No routine drainage of the peritoneal cavity |
| Patient sent to recovery ward |
| Restart oral intake of water/nutrition *ad libitum* |
| Postoperative day 1 |
| Patient sent to surgical ward |
| Patient mobilizes a minimum of four times a day |
| Discontinuation of intravenous fluids |
| Patient drinks at least 1·5 litres |
| Normal diet |
| Continue portable epidural analgesia (local anaesthetic + low-dose opioid) |
| 1000 mg paracetamol every 6 h |
| 1000 mg magnesium oxide twice daily |
| Laboratory tests |
| Postoperative day 2 |
| Continue portable epidural analgesia with local anaesthetic |
| Stop low-dose opioids |
| Continue mobilization a minimum of four times per day |
| 1000 mg paracetamol every 6 h |
| Normal diet |
| Postoperative day 3 |
| Start NSAIDs |
| Stop epidural analgesia |
| Remove urinary catheter |
| Continue mobilization |
| Normal diet |
| Laboratory tests |
| Check discharge criteria |
| Outpatient appointment made on postoperative day 10, 11 or 12 |
| Postoperative day 4 |
| Check discharge criteria (*Table 2*) |
| Patient receives mobile telephone number of operating hepatopancreatobiliary surgeon |
| Discharge |

i.v., intravenous; CVP, central venous pressure; NSAID, non-steroidal anti-inflammatory drug.

Patients in the control group were discharged without formal discharge criteria.

The following secondary endpoints were evaluated: resumption of oral intake, defined as oral intake of water or normal food without discontinuation for at least 24 h, readmissions, total morbidity, death and length of primary hospital stay, defined as the number of nights spent in hospital after surgery, excluding readmissions. Complications were registered during the primary admission or at subsequent outpatient clinic visits, after at least 6 and 30 days, using departmental liver registry databases.

**Table 2** Discharge criteria in Enhanced Recovery After Surgery liver protocol

| |
|---|
| Normal or decreasing serum bilirubin |
| Good pain control with oral analgesia only |
| Tolerance of solid food |
| No intravenous fluids |
| Mobile independently or at the preoperative level |
| All of the above and willing to go home |

**Table 3** Patient demographics

| | ERAS ($n = 61$) | Control ($n = 100$) |
|---|---|---|
| Median (range) age (years) | 62 (24–82) | 60 (20–81) |
| Sex ratio (M : F) | 35 : 26 | 51 : 49 |
| ASA grade | | |
| I | 11 (18) | 14 (14·0) |
| II | 42 (69) | 64 (64·0) |
| III | 8 (13) | 22 (22·0) |
| Liver pathology | | |
| Colorectal metastasis | 51 (84) | 72 (72·0) |
| Other metastasis | 2 (3) | 4 (4·0) |
| Hepatocellular carcinoma or cholangiocarcinoma | 4 (7) | 9 (9·0) |
| Benign lesion | 4 (7) | 14 (14·0) |
| T4 invasive tumours in liver | 0 (0) | 1 (1·0) |

Values in parentheses are percentages unless indicated otherwise. ERAS, Enhanced Recovery After Surgery; ASA, American Society of Anesthesiologists.

## Statistical analysis

Continuous data are expressed as median (range). Hospital stay, time to resumption of oral intake and postoperative duration of epidural analgesia were analysed using the Mann–Whitney $U$ test. Readmission, complication and mortality rates were analysed using $\chi^2$ test or Fisher's exact test. $P < 0{\cdot}050$ was considered to be statistically significant. Data were analysed using SPSS® version 13.0 for Windows® (SPSS, Chicago, Illinois, USA).

**Table 4** Types of liver resection

| | ERAS ($n = 61$) | Control ($n = 100$) |
|---|---|---|
| Hemihepatectomy | 20 (33) | 38 (38·0) |
| Hemihepatectomy + ≥ 1 metastasectomies | 6 (10) | 16 (16·0) |
| Extended hemihepatectomy | 7 (11) | 3 (3·0) |
| Multiple segmentectomy (≥ 2 segments) | 17 (28) | 18 (18·0) |
| Central resection/trisegmentectomy | 1 (2) | 4 (4·0) |
| Metastasectomy or monosegmentectomy | 10 (16) | 21 (21·0) |
| Repeat hepatectomy | 7 (11) | 5 (5·0) |

Values in parentheses are percentages. ERAS, Enhanced Recovery After Surgery.

## Results

Patient characteristics were similar in the ERAS and control groups (*Table 3*). Types of liver resection are shown in *Table 4*. A higher proportion of patients in the ERAS group had repeat liver resections (11 per cent *versus* 5·0 per cent in control group; $P = 0·214$) and resections after intensive chemotherapy (62 *versus* 33·0 per cent; $P < 0·001$).

The median (range) duration of surgery was 220 (60–420) min in the ERAS group and 270 (106–510) min in the control group ($P < 0·001$), and blood loss during surgery was 750 (0–5000) and 800 (0–6000) ml respectively ($P = 0·758$). Abdominal drains were used significantly less often in the ERAS group (2 *versus* 66·0 per cent; $P < 0·001$).

In Edinburgh, the use of a nasogastric decompression tube in patients having partial liver resection had already been discontinued before 1 July 2003. In Maastricht, nasogastric decompression tubes were still used in most control patients. A nasogastric tube was inserted at induction in 37 of 47 patients in the ERAS group, significantly less frequently than in the control group (96 per cent) ($P = 0·013$). In the ERAS group, the nasogastric tube was removed at the end of surgery or in the recovery ward within 4 h of surgery.

Oral intake was resumed within 4 h after surgery in 56 patients (92 per cent) in the ERAS group. Two patients required reinsertion of a nasogastric tube. The median (range) time to successful resumption of normal diet was 1 (0–3) day in the ERAS group, compared with 3 (0–14) days in controls ($P < 0·001$). Three patients in the ERAS group (5 per cent) became constipated after postoperative day 3, despite initial tolerance of normal food, but this resolved within 5 days by restricting intake.

In the ERAS group, 58 patients (95 per cent) followed the anaesthetic protocol of mid-thoracic epidural analgesia commencing before surgery (0·1 per cent bupivacaine + 2 μg/ml fentanyl) with maintenance isoflurane or sevoflurane inhalation anaesthesia, or intravenous propofol, as described previously[15]. After operation epidural analgesia comprising 0·1 per cent bupivacaine and 2 μg/ml fentanyl was administered for at least 3 days via a portable patient-controlled device (GemStar® Infusion Systems; Hospira, Lake Forest, Illinois, UK) at a rate of 4–10 ml/h, combined with oral non-opioid analgesics. This differed from anaesthesiological management in the control group, where 89 patients (89·0 per cent) received epidural analgesia combined with isoflurane or sevoflurane inhalation anaesthesia. In the postoperative period epidural analgesia consisting of 0·1 per cent bupivacaine and 2 μg/ml fentanyl was administered without a specific time schedule at a daily fixed dose of 4–10 ml/h, combined with intramuscular opioids (mainly piritramide) and oral analgesics. Postoperative epidural analgesia was continued for a median (range) of 3 (1–5) days in the ERAS group and 2 (0–6) days in the control group ($P < 0·001$). Epidural analgesia was discontinued earlier in the control group, and intramuscular or intravenous opioids (piritramide) were used more widely.

**Table 5** Outcome data

| | ERAS | Control | *P* |
|---|---|---|---|
| Maastricht only† | ($n = 47$) | ($n = 50$) | |
| NGT | 37 (79) | 48 (96) | 0·013‡ |
| Removal of NGT on day of surgery | 34 of 37 (92) | 0 (0) | < 0·001 |
| Maastricht and Edinburgh | ($n = 61$) | ($n = 100$) | |
| Epidural analgesia | 58 (95) | 89 (89·0) | 0·184‡ |
| Abdominal drain | 1 (2) | 66 (66·0) | < 0·001‡ |
| Complications | 25 (41) | 31 (31·0) | 0·197‡ |
| Death | 0 (0) | 2 (2·0) | 0·526 |
| Readmission | 8 (13) | 10 (10·0) | 0·543‡ |
| Total hospital stay, including readmissions (days)* | 6 (3–82) | 8 (4–68) | < 0·001 |
| Primary hospital stay (days)* | 6 (3–82) | 8 (4–55) | < 0·001 |

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Nasogastric tubes (NGTs) were used in Maastricht only; they were used in neither group in Edinburgh. ERAS, Enhanced Recovery After Surgery. *P* values by Fisher's exact test, except ‡$\chi^2$ test.

Outcome data are summarized in *Table 5*. There were no deaths in the ERAS group and one patient died within 30 days in the control group. A further control patient died after 62 days. Overall morbidity rates (percentage of patients with at least one complication) were 41 and 31·0 per cent in the ERAS and control groups respectively ($P = 0·197$) (*Table 6*). All complications in the ERAS group were managed by non-surgical means. Readmission rates in ERAS and control groups were similar (13 *versus* 10·0 per cent respectively; $P = 0·610$).

**Table 6** Complications

| | ERAS ($n = 61$) | Control ($n = 100$) | $P$* |
|---|---|---|---|
| No. with complications | 25 (41) | 31 (31·0) | 0.197† |
| Bile leak | 4 (7) | 4 (4·0) | 0.479 |
| Liver failure | 3 (5) | 1 (1·0) | 0.153 |
| Sepsis | 0 (0) | 1 (1·0) | 1.00 |
| Abdominal abscess | 5 (8) | 7 (7·0) | 0.779† |
| Delayed GI function (< 7 days) | 3 (5) | 1 (1·0) | 0.153 |
| Pneumonia | 3 (5) | 2 (2·0) | 0.368 |
| Pleural effusion | 2 (3) | 2 (2·0) | 0.634 |
| Pulmonary embolism | 0 (0) | 1 (1·0) | 0.433 |
| Myocardial infarction | 2 (3) | 3 (3·0) | 0.921 |
| Wound infection | 9 (15) | 5 (5·0) | 0.033† |
| Other minor | 3 (5) | 16 (16·0) | 0.018† |

Values in parentheses are percentages. ERAS, Enhanced Recovery After Surgery; GI, gastrointestinal. *Fisher's exact test, except †$\chi^2$ test.

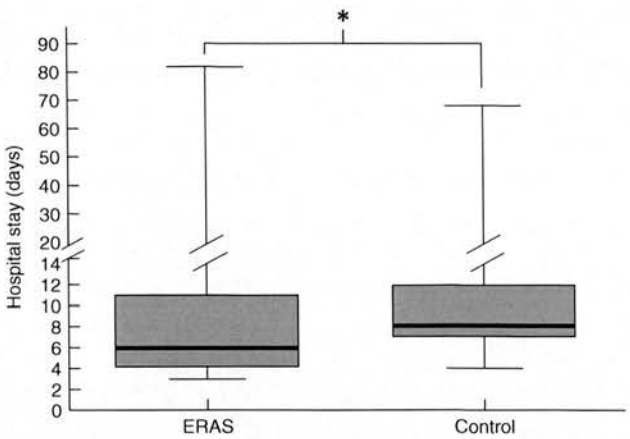



**Fig. 1** Total length of hospital stay, including readmissions, in Enhanced Recovery After Surgery (ERAS) and control groups. Horizontal lines within boxes, boxes and error bars represent median, interquartile range and total range respectively. *$P < 0·001$ (Mann–Whitney $U$ test)

Fifty-two (85 per cent) of 61 patients in the ERAS group were completely mobile on the third day after operation and 29 (48 per cent) were discharged from hospital within 5 days. Median (range) total postoperative hospital stay, including readmissions, was 6·0 (3–82) days in the ERAS group and 8·0 (4–68) days in the control group ($P < 0·001$) (*Fig. 1*).

## Discussion

The present study showed that use of an evidence-based multimodal enhanced recovery programme after liver resection accelerated postoperative recovery and led to a significantly shorter hospital stay. Patients managed according to the ERAS protocol were able to drink fluids within 4 h of liver resection and eat normal food on the day after surgery. Most patients were completely mobile after 3 days and, as a consequence, almost half of the patients were discharged from hospital within 5 days. Median total hospital stay (including readmissions) was reduced from 8 to 6 days, which is considerably shorter than the 8–14 days reported by other European centres[8–10]. Application of the ERAS protocol did not have any detrimental effect on safety in liver resection.

Based on previous experience of enhanced recovery implementation studies within these units, and attempts to randomize between fast-track and traditional care in a multicentre abdominal surgery trial[6,16], a randomized clinical trial comparing fast-track and traditional care was considered impractical. Both units had implemented ERAS protocols over the previous few years and, in view of the growing evidence base for such programmes, a traditional perioperative protocol was felt to represent suboptimal care. More importantly, it would have been necessary for nursing and surgical staff to return to traditional perioperative care pathways. Therefore, this feasibility study was designed as a prospective case series with a historical control group.

Several important issues have become apparent from this study. Importantly, adverse outcomes, assessed in terms of readmissions, complications and deaths, were similar in the ERAS and control groups. The complication rate in the ERAS group is in keeping with recently published rates of 23–52 per cent[10,17–20]. Although the morbidity rate appeared to be higher in the ERAS group, the study was not sufficiently powered to determine statistical differences in the incidence of complications. Moreover, complications directly related to liver surgery, such as bleeding, bile leakage or temporary liver failure, are unlikely to be influenced by postoperative care. Avoidance of abdominal drains in this study might arguably have influenced the complication rate, but the authors consider this unlikely because the incidence of bile leak and intra-abdominal abscess was similar in the two groups. Prophylactic drains are employed in many centres to detect early complications such as postoperative haemorrhage or bile leakage, to remove intraperitoneal fluids and to prevent abscess formation. However, there is evidence that abdominal drainage after liver resection does not reduce the incidence of reinterventions for these complications[21–23]. Some studies have even noted higher rates of infected collections when drainage was used[13,21,24]. This suggests that drains might be detrimental to clinical outcome by providing a route for ascending infections. Another disadvantage of drains within an enhanced recovery setting

is that they represent a significant impediment to achieving early mobilization.

A few elements have proven difficult to implement universally. The use of carbohydrate drinks before surgery reduces thirst, hunger and anxiety, and is safe up to 2 h before abdominal surgery[25]. However, a preoperative fasting policy of 'nil by mouth from midnight' is still common. Owing to tradition in the anaesthesia department nasogastric decompression tubes were still used extensively during surgery in both groups in Maastricht, but were removed immediately after surgery in the ERAS group. This practice meant a major change in clinical routines, and did not appear to result in more pulmonary complications in the present study. In general, nasogastric decompression is still used widely following abdominal surgery[26], despite evidence that it is unnecessary and can result in more pulmonary complications. Further support for avoidance of nasogastric tubes specifically in liver surgery has been published recently[11].

Early postoperative enteral nutrition compared with 'nil by mouth' improves clinical outcome[27]. In the present study, oral intake of water within 4 h after surgery and institution of normal nutrition on the day after operation were well tolerated in the ERAS group. Early resumption of normal diet in combination with other elements of the enhanced recovery programme is designed to reduce the occurrence of delayed gastrointestinal function after surgery and even promote appetite. Therefore, the ability of the patient to tolerate normal food is an outcome in itself. A period of delayed gastrointestinal functioning after operation, observed in a few patients, was registered as a complication. It might also be argued that a delay in gastrointestinal functioning is a physiological phenomenon that occurs after abdominal surgery in many patients. A restrictive perioperative intravenous fluid regimen may help to reduce the occurrence of delayed gastrointestinal functioning[28]. Fluid restriction may well be an important issue in hepatic surgery and is the subject of ongoing research in the authors' units.

It is important that surgical patients are treated in an environment that encourages early mobilization[4]. Mobilization on the day of surgery was possible in Edinburgh, but was not achieved in Maastricht because the recovery unit did not contain the appropriate facilities. Adequate pain control and a substantial effort by nursing staff are required to achieve early mobilization.

In conclusion, a multimodal enhanced recovery programme for patients undergoing liver resection for primary and secondary tumours, but with otherwise normal hepatic function, is feasible and effective. Patients were able to drink within 4 h of surgery, eat on the following day and were usually mobile by the third day after operation. This is indicative of earlier recovery and was accompanied by a 25 per cent reduction in postoperative hospital stay. The fact that only half of the patients were discharged within 5 days indicates that there is further room for improvement.

## Acknowledgements

The ERAS group thanks the patients who participated in the study, and the surgeons, anaesthetists and nursing colleagues who helped deploy the protocol. The group also thanks Mrs J. Maessen, Mrs M. J. T. Kleijnen-van't Hullenaer and Mrs K. M. L. Luyten, who played a key role in implementation of the ERAS protocol at the surgical ward in Maastricht.

The ERAS collaboration and the preparatory meetings leading to this study were supported by an unrestricted grant from Nutricia Healthcare, The Netherlands. The participants from Maastricht acknowledge financial support by an unrestricted grant from Nycomed, The Netherlands. C.H.C.D. was supported by a grant from the Dutch Organization for Health Research and Development (NWO Clinical Fellowship 907-00-033).

## References

1 Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; **362**: 1921–1928.
2 Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K *et al.* Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr* 2005; **24**: 466–477.
3 Podore PC, Throop EB. Infrarenal aortic surgery with a 3-day hospital stay: a report on success with a clinical pathway. *J Vasc Surg* 1999; **29**: 787–792.
4 Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002; **183**: 630–641.
5 Nygren J, Hausel J, Kehlet H, Revhaug A, Lassen K, Dejong C *et al.* A comparison in five European Centres of case mix, clinical management and outcomes following either conventional or fast-track perioperative care in colorectal surgery. *Clin Nutr* 2005; **24**: 455–461.
6 Maessen J, Dejong CH, Hausel J, Nygren J, Lassen K, Andersen J *et al.* A protocol is not enough to implement an enhanced recovery programme for colorectal resection. *Br J Surg* 2007; **94**: 224–231.
7 Cerfolio RJ, Bryant AS, Bass CS, Alexander JR, Bartolucci AA. Fast tracking after Ivor Lewis esophagogastrectomy. *Chest* 2004; **126**: 1187–1194.
8 Capussotti L, Muratore A, Ferrero A, Massucco P, Ribero D, Polastri R. Randomized clinical trial of liver resection with and without hepatic pedicle clamping. *Br J Surg* 2006; **93**: 685–689.

9 Dimick JB, Wainess RM, Cowan JA, Upchurch GR JR, Knol JA, Colletti LM. National trends in the use and outcomes of hepatic resection. *J Am Coll Surg* 2004; **199**: 31–38.

10 Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S *et al.* Improvement in perioperative outcome after hepatic resection: analysis of 1803 consecutive cases over the past decade. *Ann Surg* 2002; **236**: 397–406.

11 Pessaux P, Regimbeau JM, Dondero F, Plasse M, Mantz J, Belghiti J. Randomized clinical trial evaluating the need for routine nasogastric decompression after elective hepatic resection. *Br J Surg* 2007; **94**: 297–303.

12 Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg* 2000; **191**: 38–46.

13 Burt BM, Brown K, Jarnagin W, DeMatteo R, Blumgart LH, Fong Y. An audit of results of a no-drainage practice policy after hepatectomy. *Am J Surg* 2002; **184**: 441–445.

14 Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg* 2005; **12**: 351–355.

15 van de Poll MC, Siroen MP, Van Leeuwen PA, Soeters PB, Melis GC, Boelens PG *et al.* Interorgan amino acid exchange in humans: consequences for arginine and citrulline metabolism. *Am J Clin Nutr* 2007; **85**: 167–172.

16 Wind J, Hofland J, Preckel B, Hollmann MW, Bossuyt PM, Gouma DJ *et al.* Perioperative strategy in colonic surgery; LAparoscopy and/or FAst track multimodal management versus standard care (LAFA trial). *BMC Surg* 2006; **6**: 16.

17 Petrowsky H, McCormack L, Trujillo M, Selzner M, Jochum W, Clavien PA. A prospective, randomized, controlled trial comparing intermittent portal triad clamping *versus* ischemic preconditioning with continuous clamping for major liver resection. *Ann Surg* 2006; **244**: 921–928.

18 Figueras J, Llado L, Miro M, Ramos E, Torras J, Fabregat J *et al.* Application of fibrin glue sealant after hepatectomy does not seem justified: results of a randomized study in 300 patients. *Ann Surg* 2007; **245**: 536–542.

19 Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. *Ann Surg* 2006; **243**: 373–379.

20 Benzoni E, Cojutti A, Lorenzin D, Adani GL, Baccarani U, Favero A *et al.* Liver resective surgery: a multivariate analysis of postoperative outcome and complication. *Langenbecks Arch Surg* 2007; **392**: 45–54.

21 Fong Y, Brennan MF, Brown K, Heffernan N, Blumgart LH. Drainage is unnecessary after elective liver resection. *Am J Surg* 1996; **171**: 158–162.

22 Petrowsky H, Demartines N, Rousson V, Clavien PA. Evidence-based value of prophylactic drainage in gastrointestinal surgery: a systematic review and meta-analyses. *Ann Surg* 2004; **240**: 1074–1084.

23 Belghiti J, Kabbej M, Sauvanet A, Vilgrain V, Panis Y, Fekete F. Drainage after elective hepatic resection. A randomized trial. *Ann Surg* 1993; **218**: 748–753.

24 Liu CL, Fan ST, Lo CM, Wong Y, Ng IO, Lam CM *et al.* Abdominal drainage after hepatic resection is contraindicated in patients with chronic liver diseases. *Ann Surg* 2004; **239**: 194–201.

25 Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications. *Cochrane Database Syst Rev* 2003; (4)CD004423.

26 Kehlet H, Buchler MW, Beart RW JR, Billingham RP, Williamson R. Care after colonic operation – is it evidence-based? Results from a multinational survey in Europe and the United States. *J Am Coll Surg* 2006; **202**: 45–54.

27 Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding *versus* 'nil by mouth' after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. *BMJ* 2001; **323**: 773–776.

28 Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; **359**: 1812–1818.


If you wish to comment on this, or any other article published in the *BJS*, please visit the on-line correspondence section of the website (www.bjs.co.uk). Electronic communications will be reviewed by the Correspondence Editor and a selection will appear in the correspondence section of the Journal. Time taken to produce a thoughtful and well written letter will improve the chances of publication in the Journal.

Original article

# Determinants of outcome after colorectal resection within an enhanced recovery programme

**P. O. Hendry[1], J. Hausel[2], J. Nygren[2], K. Lassen[3], C. H. C. Dejong[4], O. Ljungqvist[5] and K. C. H. Fearon[1], on behalf of the Enhanced Recovery After Surgery (ERAS) Study Group**

[1]Edinburgh Royal Infirmary, Edinburgh, UK, [2]Ersta Hospital, Stockholm, Sweden, [3]University Hospital Northern Norway, and University of Tromsø, Tromsø, Norway, [4]University Hospital Maastricht and NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University, Maastricht, The Netherlands, and [5]Karolinska Institute, Stockholm, Sweden

*Correspondence to:* Mr P. O. Hendry, Royal Infirmary, 51 Little France Crescent, Edinburgh EH16 4SA, UK (e-mail: paul.hendry@ed.ac.uk)

**Background:** **Postoperative outcomes were studied in relation to adverse nutritional risk (body mass index (BMI) below 20 kg/m$^2$), advanced age (80 years or more) and co-morbidity (American Society of Anesthesiologists (ASA) grade III–IV) in patients undergoing colorectal resection within an enhanced recovery after surgery programme.**

**Methods:** **Outcomes were audited prospectively in 1035 patients. Morbidity and mortality were compared with those predicted using the Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity, and a multivariable model was used to determine independent predictors of outcome.**

**Results:** **Postoperative morbidity was lower than predicted (observed to expected 0·68; $P < 0·001$). Independent predictors of delayed mobilization were ASA III–IV ($P < 0·001$) and advanced age ($P = 0·025$). Prolonged hospital stay was related to advanced age ($P = 0·002$), ASA III–IV ($P < 0·001$), male sex ($P = 0·037$) and rectal surgery ($P < 0·001$). Morbidity was related to ASA III–IV ($P = 0·004$), male sex ($P = 0·023$) and rectal surgery ($P = 0·002$). None of the factors predicted 30-day mortality.**

**Conclusion:** **Age and nutritional status were not independent determinants of morbidity or mortality. Pre-existing co-morbidity was an independent predictor of several outcomes.**

Presented in part to a conference of the European Society for Clinical Nutrition and Metabolism in Prague, Czech Republic, September 2007

Paper accepted 13 October 2008

Published online in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.6445

## Introduction

Patients undergoing major abdominal surgery are thought to be at increased risk of delayed recovery, morbidity and death owing to factors such as age, undernutrition and co-morbidity. This increased risk may be due to the combined effects of tissue wasting, impaired immune function, impaired healing and organ dysfunction[1,2]. The links between advanced age or poor nutritional status and adverse surgical outcome have long been recognized[3–5]. Although it may be argued that modern surgery with prophylactic antibiotics, better analgesia, improved suture materials and high-dependency postoperative care might avoid such adverse outcomes, recent studies involving traditional perioperative care show a similar relationship[6,7]. Indeed, a recent study showed that in-hospital mortality for patients aged over 85 years undergoing colorectal surgery was nine times higher than that for those aged 65 years or less[8].

Although recent epidemiological evidence suggests that there is an epidemic of obesity[9], a significant proportion of the surgical population remain undernourished and potentially at increased risk[10]. Likewise, it is evident that the general population is getting older. In the USA life expectancy is 7 years for the average 80-year-old man and nine years for the average 80-year-old woman[11]. In such elderly patients, increased morbidity and mortality after surgery is thought to result from a lack of organ function and/or reserve to sustain the patient in the

The Editors are satisfied that all authors have contributed significantly to this publication

event of complications[4]. However, it is often difficult to discriminate between the risks attributable primarily to a single factor (for example age) and the compounding effects of other co-variables (such as increased co-morbidity with old age).

Enhanced recovery after surgery (ERAS) protocols are designed to reduce the surgical stress response and support basic body functions by the use of optimized analgesia, early mobilization and early return to normal diet[12,13]. These interventions have been shown to improve postoperative outcomes[14,15]. The elderly appear to be at particular risk of death once a postoperative complication has developed[7]. It is therefore of interest that a recent systematic analysis of enhanced recovery has suggested that an ERAS programme may favourably influence postoperative morbidity[15] and so might be a particularly useful prophylactic measure for elderly patients.

As part of a study examining the feasibility, efficacy and safety of an ERAS protocol for elective open colorectal surgery, observed morbidity and mortality rates were compared with rates predicted by the Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (P-POSSUM)[16]. In addition, the prognostic value of body mass index (BMI), age, American Society of Anesthesiologists (ASA) grade, malignancy status, sex and operation type was investigated.

## Methods

Between March 2002 and December 2005 patients aged 18–94 years undergoing elective open colorectal surgery with formation of an anastomosis (at or above the peritoneal reflection) were included. The upper limit of the rectum was considered to be level with the sacral promontory. Patients with rectal cancer were included if the tumour was in the upper third of the rectum and allowed anastomosis in the middle third of the rectum (at or about the level of the peritoneal reflection). Patients requiring total mesorectal excision were excluded. Most sigmoid and all rectosigmoid and upper rectal tumours underwent formal anterior resection with high ligation of the vessels and take-down of the splenic flexure. Patients with benign or malignant pathology and with an ASA grade of I–IV were included in the study. Four departments of surgery in Northern Europe (University Hospital, Maastricht, The Netherlands; University Hospital Northern Norway, Tromsø, Norway; Karolinska Institute at Ersta Hospital, Stockholm, Sweden; Western General Hospital, Edinburgh, UK) participated for a minimum of 12 months. Ethical approval and informed written consent was obtained from all patients in centres where de-identification of data did not provide dispensation of this obligation.

All patients followed an ERAS protocol based on continuous thoracic epidural anaesthesia/analgesia, early mobilization and resumption of diet, and nutritional supplements as described previously[12] (*Fig. 1*). Mechanical bowel preparation was not used routinely, but was applied mainly before left-sided or anterior resections. Compliance was audited prospectively.

### Measurements

In all centres data were collected prospectively on a computerized database as described previously[17]. Data included patient demographics (including preoperative BMI), surgical procedures and postoperative outcomes (including time to achieve targeted mobility, total length of hospital stay, complications and 30-day mortality). Follow-up for morbidity and mortality was verified either during the primary admission, by telephone contact at 30 days or at subsequent outpatient clinic visits.

Time to achieve targeted mobilization was defined as the number of days after surgery until the patient was out of bed for more than 6 h per day and at the same level of independence with respect to daily living as before surgery. Total hospital stay was defined as the number of nights spent in hospital after surgery, including nights after readmission within 30 days after surgery. To determine the influence of complications on postoperative recovery and hospital stay, all adverse events in the postoperative period were recorded prospectively as described previously[18]. The postoperative course was considered complicated if any complication by accepted standard definitions occurred[19,20].

Patients were grouped according to preoperative BMI (World Health Organization categories[9]) as an indicator of preoperative nutritional status. Given the elderly nature of the overall population a BMI below 20 kg/m$^2$ was considered to indicate a risk of undernutrition. Patients were also grouped according to age (less than 80 years, 80 or more years) and ASA grade (low, I–II; high, III–IV).

### Morbidity and mortality analysis

Predicted (expected, E) morbidity and mortality were based on P-POSSUM scoring[16] and compared with observed (O) morbidity and mortality recorded up to 30 days after surgery. Results were expressed as O : E ratios. Missing values (less than 5 per cent of all variables) for P-POSSUM were assumed to be normal.

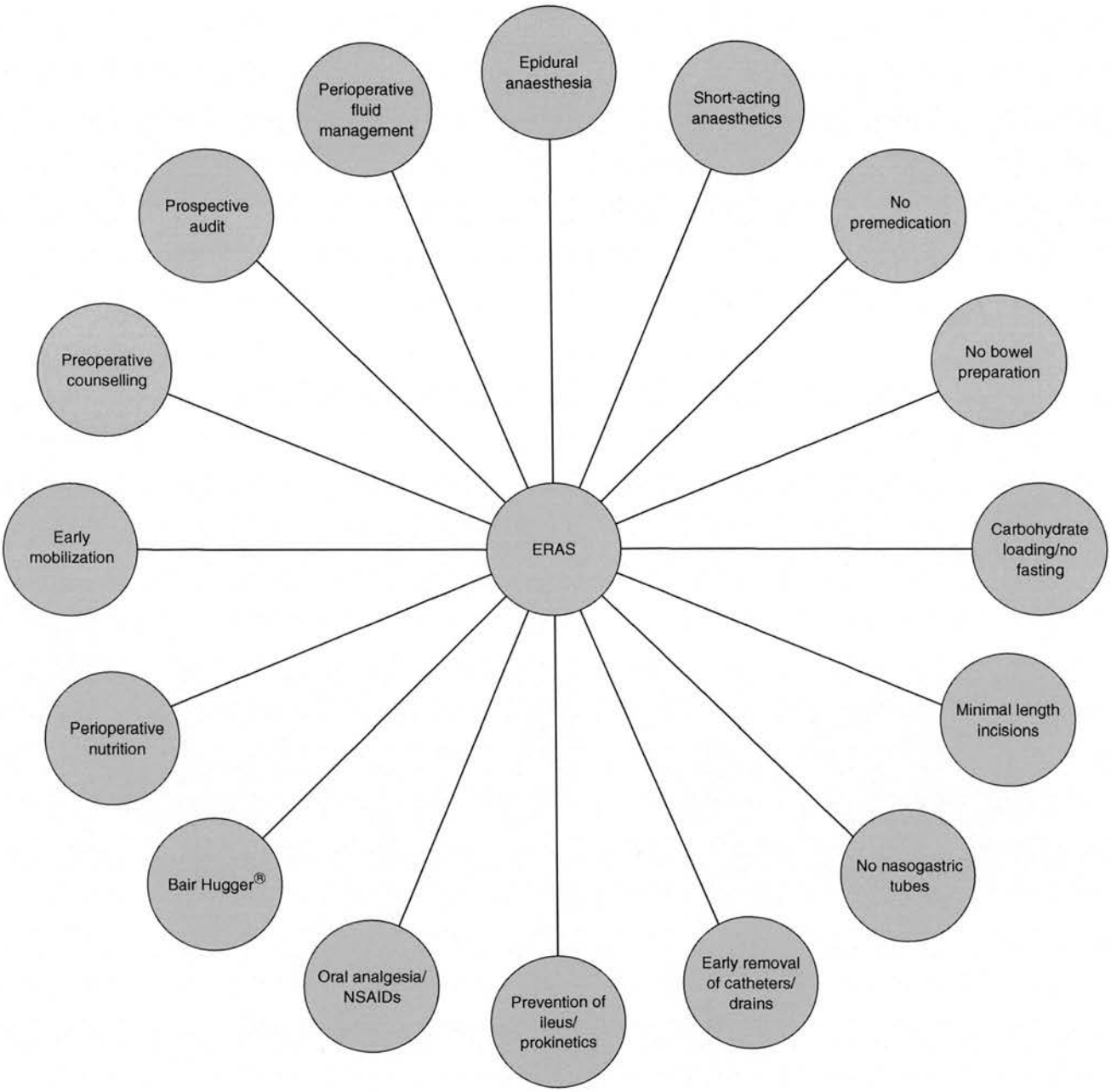



**Fig. 1** Summary of enhanced recovery after surgery (ERAS) protocol elements. Bair Hugger®, Arizant, Wakefield, UK. NSAID, non-steroidal anti-inflammatory drug

## Statistical analysis

SPSS® version 16 for Mac (SPSS, Chicago, Illinois, USA) was used for data analysis. Data were collected prospectively to assess the efficacy of the ERAS programme and included all patients undergoing elective colorectal resection with an ASA grade I–IV. Before introduction of this ERAS programme there were few morbidity and mortality data on which to base a sample size calculation, and no such calculation was undertaken.

The data set was analysed using time to achieve mobilization, total hospital stay, complication rates and 30-day mortality as the main outcome variables. Factors

possibly influencing these variables included: sex, age (less than 80 years, 80 or more years), type of surgery (colonic, rectal), presence of malignancy, BMI (less than 20 kg/m$^2$, at least 20 kg/m$^2$) and co-morbidity (ASA I–II, III–IV). Univariable analysis was initially undertaken to assess the relationship between each factor and the outcome variables. Comparisons were made using the $\chi^2$ test or Fisher's exact test, as appropriate, for all categorical variables and the Mann–Whitney $U$ test for continuous variables. Multivariable analysis, using binary logistic regression for categorical variables and linear regression of log transformed continuous variables, was then performed for all variables with a significant or near-significant difference ($P < 0{\cdot}150$) in univariable analysis. In multivariable analysis non-significant factors were excluded sequentially and the model re-run. $P < 0{\cdot}050$ was considered statistically significant.

## Results

A total of 1035 patients followed the ERAS protocol. Compliance with preoperative and intraoperative elements of the protocol was high; 87·5 per cent of patients received preoperative counselling and instruction, 63·4 per cent completed carbohydrate loading and 87·6 per cent received epidural analgesia/anaesthesia. Protocol compliance in the postoperative phase was lower; intravenous fluids were discontinued on the day after surgery in 44·3 per cent, 39·2 per cent were out of bed on the day of surgery, and 61·4 per cent resumed a full diet on the day after surgery. Overall demographics and outcomes are shown in *Table 1*. The male to female ratio was 498 : 537 and 68·6 per cent were treated for malignant disease. There were 724 colonic and 311 rectal resections. Some 7·9 per cent of patients had a BMI below 20 kg/m$^2$, 18·7 per cent were aged 80 years or more, and 20·6 per cent had an ASA grade of III–IV.

The overall median time to achieve targeted mobilization was 3 days and total hospital stay was 6 days. The overall readmission rate was 8·6 per cent, the reoperation rate was 7·4 per cent and the anastomotic leak rate was 5·1 per cent. The morbidity rate for the whole group was significantly lower than that predicted by P-POSSUM (O : E 0·68; $P < 0{\cdot}001$), whereas 30-day mortality was not significantly different from the predicted value (O : E 0·68; $P = 0{\cdot}212$). Patients undergoing rectal resection had a longer hospital stay and a higher overall complication rate than those having colonic surgery. In contrast, O : E morbidity and mortality tended to be higher in the colonic group.

Complications are summarized in *Table 2*. The most frequent complications were infective, including wound and urinary tract infections. Patients most commonly developed only a single complication. A higher proportion of patients developed one or more complications after receiving mechanical bowel

**Table 1** Patient demographics and outcomes

| | All patients ($n = 1035$) | Colonic ($n = 724$) | Rectal ($n = 311$) | $P$† |
|---|---|---|---|---|
| Sex ratio (M : F) | 498 : 537 | 340 : 384 | 158 : 153 | 0·257‡ |
| Age (years)* | 59 (69–78) | 71 (59–79) | 65 (57–75) | < 0·001§ |
| ASA grade | | | | |
| I | 177 (17·1) | 107 (14·8) | 70 (22·5) | |
| II | 645 (62·3) | 464 (64·1) | 181 (58·2) | |
| III | 203 (19·6) | 144 (19·9) | 59 (19·0) | |
| IV | 10 (1·0) | 9 (1·2) | 1 (0·3) | < 0·001¶ |
| Malignant disease | 710 (68·6) | 501 (69·2) | 209 (67·2) | 0·481‡ |
| Neoadjuvant therapy | 15 (1·4) | 5 (0·7) | 10 (3·2) | 0·004‡ |
| Time to mobilization (days)* | 3 (2–5) | 3 (2–5) | 3 (2–5) | 0·191§ |
| Total hospital stay (days)* | 6 (4–8) | 6 (4–8) | 7 (5–10) | < 0·001§ |
| Readmission | 86 (8·6) | 57 (7·9) | 29 (9·3) | 0·444‡ |
| Anastomotic leak | 53 (5·1) | 37 (5·1) | 16 (5·1) | 0·982‡ |
| Reoperation | 77 (7·4) | 56 (7·7) | 21 (6·7) | 0·563‡ |
| 30-day morbidity | 294 (28·4) | 185 (25·6) | 109 (35·0) | < 0·001‡ |
| 30-day mortality | 17 (1·6) | 14 (1·9) | 3 (1·0) | 0·423‡ |
| Expected morbidity | 430 (41·5) | 259 (35·8) | 171 (55·0) | < 0·001‡ |
| Expected mortality | 25 (2·4) | 14 (1·9) | 11 (3·5) | 0·156‡ |
| O : E morbidity | 0·68 | 0·71 | 0·64 | |
| O : E mortality | 0·68 | 1·00 | 0·27 | |

Values in parentheses are percentages unless indicated otherwise; *values are median (interquartile range). ASA, American society of Anesthesiologists; O : E, observed to expected. †Colonic *versus* rectal; ‡$\chi^2$ test; §Mann–Whitney $U$ test; ¶Fisher's exact test.

**Table 2** Complications in 1035 patients

| | No. of patients |
|---|---|
| Respiratory failure | 23 (2·2) |
| Pulmonary oedema | 4 (0·4) |
| Pulmonary embolism | 6 (0·6) |
| Cardiac failure | 22 (2·1) |
| Acute myocardial infarction | 3 (0·3) |
| Stroke | 2 (0·2) |
| Deep vein thrombosis | 1 (0·1) |
| Acute renal failure | 6 (0·6) |
| Wound dehiscence | 28 (2·7) |
| Postoperative bleeding | 29 (2·8) |
| Anastomotic leak | 53 (5·1) |
| Wound infection | 128 (12·4) |
| Pneumonia | 24 (2·3) |
| Chest infection | 15 (1·4) |
| Sepsis | 18 (1·7) |
| Urinary tract infection | 67 (6·5) |

Values in parentheses are percentages. A total of 741 patients had no complication; 213, 45, 23, eight and five patients had one, two, three, four and five complications respectively.

preparation (184 (30·9 per cent) of 596 *versus* 106 (24·9 per cent) of 425 patients having no mechanical bowel preparation; $P = 0·041$). There were no differences in anastomotic leak rates or 30-day mortality between those who did or did not receive mechanical bowel preparation.

The results of univariable analysis of the relationship between outcomes and potential outcome predictors are shown in *Table 3*. BMI category was not related to any of the outcome variables. Age had an influence on time to achieve mobilization ($P < 0·001$) and total hospital stay ($P < 0·001$). There was a significant relationship between ASA grade and mobilization ($P < 0·001$), total hospital stay ($P < 0·001$) and postoperative morbidity rate ($P = 0·003$). Sex influenced postoperative morbidity rate ($P = 0·011$). Operation type affected total hospital stay ($P < 0·001$) and postoperative morbidity rate ($P = 0·002$). The presence of malignancy did not relate to any of the outcomes.

In multivariable analysis independent predictors of prolonged mobilization were age 80 years or more ($P = 0·025$) and ASA grade III–IV ($P < 0·001$). Prolonged total length of hospital stay was predicted by age 80 years or more ($P = 0·002$), ASA grade III–IV ($P < 0·001$), male sex ($P = 0·037$) and rectal surgery ($P < 0·001$). Postoperative morbidity was predicted by ASA grade III–IV ($P = 0·004$), male sex ($P = 0·023$) and rectal surgery ($P = 0·002$). Mortality was not related to any of the factors.

**Table 3** Univariable analysis of postoperative outcomes

| | No. of patients | Time to mobilization (days)* | Total hospital stay (days)* | 30-day morbidity† | 30-day mortality† |
|---|---|---|---|---|---|
| Body mass index (kg/m$^2$) | | | | | |
| < 20 | 82 | 3 (2–4) | 6 (4–8) | 27 (33) | 1 (1) |
| ≥ 20 | 953 | 3 (2–5) | 6 (4–8) | 267 (28·0) | 16 (1·7) |
| *P* | | 0·791‡ | 0·820‡ | 0·344§ | 1·000¶ |
| Age (years) | | | | | |
| < 80 | 839 | 3 (2–5) | 6 (4–8) | 229 (27·3) | 11 (1·3) |
| ≥ 80 | 194 | 4 (2–6) | 7 (5–11) | 64 (33·0) | 6 (3·1) |
| *P* | | < 0·001‡ | < 0·001‡ | 0·113§ | 0·109¶ |
| ASA grade | | | | | |
| I–II | 822 | 3 (2–5) | 6 (4–8) | 216 (26·3) | 11 (1·3) |
| III–IV | 213 | 4 (3–6) | 7 (5–12·5) | 78 (36·6) | 6 (2·8) |
| *P* | | < 0·001‡ | < 0·001‡ | 0·003§ | 0·133¶ |
| Sex | | | | | |
| M | 498 | 3 (2–5) | 6 (4–9) | 160 (32·1) | 11 (2·2) |
| F | 537 | 3 (2–5) | 6 (4–8) | 134 (25·0) | 6 (1·1) |
| *P* | | 0·986‡ | 0·123‡ | 0·011§ | 0·168¶ |
| Type of surgery | | | | | |
| Colonic | 724 | 3 (2–5) | 6 (4–8) | 185 (25·6) | 14 (1·9) |
| Rectal | 311 | 3 (2–5) | 7 (5–10) | 109 (35·0) | 3 (1·0) |
| *P* | | 0·191‡ | < 0·001‡ | 0·002§ | 0·255§ |
| Type of lesion | | | | | |
| Malignant | 313 | 3 (2–4) | 6 (4–8) | 88 (28·1) | 2 (0·6) |
| Benign | 710 | 3 (2–5) | 6 (4–9) | 203 (28·6) | 13 (1·8) |
| *P* | | 0·067‡ | 0·161‡ | 0·876§ | 0·254¶ |

*Values are median (interquartile range); †values in parentheses are percentages. ASA, American society of Anesthesiologists. ‡Mann–Whitney *U* test; § $\chi^2$ test; ¶Fisher's exact test.

## Discussion

In this study the overall morbidity rate was 28·4 per cent and the mortality rate was 1·6 per cent after colorectal resection. Morbidity was significantly lower than that predicted by the P-POSSUM system whereas mortality was similar to the predicted value. Morbidity and mortality rates in this cohort were lower than those published for the same units before the introduction of an ERAS protocol (35 and 2 per cent respectively)[18] and for other European units following traditional care pathways (35–38·3 and up to 3·4 per cent respectively)[21,22]. These findings attest to the safety and potential benefits of the ERAS approach to perioperative care. Median length of hospital stay was 6 days, which is below that published for similar series using traditional care in combination with either open[18] or laparoscopic[21,23,24] techniques. The readmission rate of 8·6 per cent was higher than that associated with traditional perioperative care[18], but was considerably lower than the rate of 20–25 per cent reported for the seminal fast-track programme in Denmark[25].

There was good compliance with the preoperative and intraoperative elements of the programme, but adherence to the protocol fell in the postoperative phase, as noted previously[17]. Postoperative variables are both markers of protocol compliance and markers of recovery. Patients achieving the postoperative goals of the protocol are likely to be those making good progress and potentially an accelerated postoperative recovery.

Against a background of favourable clinical outcomes obtained with the ERAS protocol, the present study demonstrated that neither BMI below 20 kg/m$^2$ nor age 80 years or more was an independent predictor of postoperative 30-day morbidity or mortality. The present results therefore suggest that in the context of an enhanced recovery programme the surgeon does not need to individualize postoperative morbidity or mortality risk assessment for elderly or undernourished patients. In contrast, co-morbidity was a consistent independent determinant for a range of outcomes.

The mortality rate for those aged 80 years or above was 3·1 per cent in this study. The outcome from elective colorectal surgery in such elderly patients is variable, with reported rates from single institutions as low as 1·1 per cent[26] and from national studies as high as 11·3 per cent[27]. When patients have been managed using traditional perioperative care, age has been demonstrated repeatedly to be a significant independent predictor of increased mortality after colorectal surgery, even when elderly patients have been selected as 'fit for surgery'[28,29]. Advanced age has also been related to increased postoperative morbidity[6], and postoperative pulmonary and renal complications in the elderly have been shown to be independent predictors of decreased long-term survival[30]. However, for older patients who make it through the immediate postoperative period, 5-year survival of those aged 80 years or more is similar to that of the younger group[31]. This has led to a call for improving perioperative care of elderly patients, including measures to minimize in-hospital postoperative complications[30]. The results of the present study suggest that age is no longer an independent risk factor for mortality when patients are managed within an enhanced recovery programme. This is in keeping with a recent meta-analysis[15], and suggests that the principles of relatively stress-free surgery and minimization of organ dysfunction translate into reduced morbidity and decreased risk of surgery in the elderly.

Elderly patients are a heterogeneous group and the use of age to predict surgical outcome may be confounded by differences in cancer stage[29], tumour site and, most significantly, increased co-morbidity. However, age is not always associated with increased co-morbidity and excellent outcomes after major surgery in the elderly have been documented[26]. In this present series, age was significantly related only to time to achieve targeted mobilization and total hospital stay. The increase in length of hospital stay might be attributed to delayed discharge related to difficulties in arranging social care[17,32].

In the UK, current guidelines suggest that all patients admitted for major abdominal surgery should undergo nutritional screening (National Institute for Health and Clinical Excellence perioperative guidelines[33]). The basis for this recommendation lies in the observation that malnourished patients are at increased risk of postoperative morbidity and mortality, and that nutritional support might attenuate such risk. However, routine preoperative nutritional screening has been difficult to achieve and one UK study noted that it took place in only 33 per cent of patients[34]. The present study demonstrated that low BMI is not an independent risk factor for adverse outcome when patients are managed within an ERAS programme and so nutritional screening may not be required. Indeed, the metabolic and nutritional elements of the ERAS protocol are designed to minimize catabolism[35]. However, there are clear limitations to the use of BMI for screening nutritional status. Some patients weigh less than is usual for their height but are otherwise fit and healthy, and a normal BMI does not exclude the presence of malnutrition. Despite these limitations, BMI is regarded generally as a robust 'field' method, especially within a large population. BMI is used as part of the nutritional assessment guidelines of the European Society for Clinical Nutrition and Metabolism[36] and in the Malnutrition Universal Screening Tool[37]

published by the British Association for Parenteral and Enteral Nutrition.

Co-morbidity is a significant predictor of postoperative outcomes after open surgery (with traditional perioperative care) as evidenced by its use in the POSSUM scoring system[16], the ASA risk stratification system and, most recently, the simplified risk stratification system[38]. The present study confirms such findings for open surgery combined with enhanced recovery. It has been suggested previously that ERAS programmes might benefit those with significant cardiorespiratory or renal co-morbidity[39], and this benefit might be most evident in vulnerable subgroups such as the elderly. The present study demonstrated lower morbidity rates with use of an ERAS protocol even though 20·6 per cent of patients had significant co-morbidity (ASA III or IV). Thus, although co-morbidity is still a highly relevant predictor of outcome, it may be modulated beneficially by the ERAS approach.

Rectal surgery and male sex were identified as independent predictors of total length of hospital stay and postoperative morbidity. These associations could be explained by the known increased risk in rectal surgery itself and the greater difficulties of dissection in the male pelvis[40]. The present data set was initiated at a time when there was uncertainty about the value of mechanical bowel preparation. Patients who received mechanical bowel preparation had a significantly greater complication rate than those who did not, consistent with the current literature[41]. The ERAS protocol now recommends the use of mechanical bowel preparation only in specific circumstances (such as low anterior resection with a covering ileostomy).

An ERAS protocol represents an overall strategy to condition all patients, and to improve all aspects of perioperative care and outcome. The present study lends support to this approach. The challenge remains how to optimize the ERAS protocol further. These results suggest that a focus on improvement of organ function impaired by common causes of co-morbidity may be one route forward.

## Acknowledgements

Current members of ERAS Study Group: C. H. C. Dejong, K. C. H. Fearon, J. Hausel, R. Kennedy, K. Lassen, O. Ljungqvist, D. N. Lobo, J. Maessen, M. F. von Meyenfeldt, J. Nygren, A. Revhaug and C. Spies.

The authors thank Miss C. Graham for statistical advice in the preparation of this manuscript, the patients who agreed to participate in the study, and the surgeons, anaesthetists and nursing colleagues who helped implement the protocol: S. Nimmo, D. Brown, D. Bartolo and the late A. McGregor in the UK; H. Willigers, M. Bemelmans, R. van Dam and G. Beets in the Netherlands; M. Soop in Sweden; T. Pedersen, P. A. Nilsen and T. Arntsen in Norway. They also thank A. Balfour, R. Luff, E. Franden and K. Fosland who played a key role in implementation of the protocol and collection of the primary prospective data.

The ERAS collaboration and the preparatory meetings leading to this study were supported by an unrestricted grant from Nutricia Healthcare, The Netherlands. The ERAS group is currently supported by an unrestricted grant from Fresenius-Kabi. C.H.C.D. was supported by a grant from the Netherlands Organization for Health Research and Development (NWO Clinical Fellowship 907-00-033). The work at Ersta Hospital was supported, in part, by the Swedish Research Council (no. 09101), Stockholm County Council and the Sodenbergs Foundation. The authors declare no other conflict of interest.

## References

1 Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. *Am Rev Respir Dis* 1982; **126**: 5–8.
2 Giner M, Laviano A, Meguid MM, Gleason JR. In 1995 a correlation between malnutrition and poor outcome in critically ill patients still exists. *Nutrition* 1996; **12**: 23–29.
3 Studley HO. Percentage of weight loss with physical impairment: a basic indicator of surgical risk in patients with chronic peptic ulcer. *JAMA* 1936; **106**: 458–460.
4 Ergina PL, Gold SL, Meakins JL. Perioperative care of the elderly patient. *World J Surg* 1993; **17**: 192–198.
5 Hill GL. Impact of nutritional support on the clinical outcome of the surgical patient. *Clin Nutr* 1994; **13**: 331–340.
6 Polanczyk CA, Marcantonio E, Goldman L, Rohde LE, Orav J, Mangione CM *et al.* Impact of age on perioperative complications and length of stay in patients undergoing noncardiac surgery. *Ann Intern Med* 2001; **134**: 637–643.
7 Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. *J Am Geriatr Soc* 2005; **53**: 424–429.
8 Fazio V, Tekkis P, Remzi F, Lavery I. Assessment of operative risk in colorectal cancer surgery: the Cleveland Clinic Foundation colorectal cancer model. *Dis Colon Rectum* 2004; **47**: 2015–2024.
9 World Health Organization (WHO). *Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation.* Technical Report Series no. 894. WHO: Geneva, 2000.
10 Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral

nutritional supplements postoperatively in malnourished surgical patients. *Gut* 2000; **46**: 813–818.
11 Manton KG, Vaupel JW. Survival after the age of 80 in the United States, Sweden, France, England, and Japan. *N Engl J Med* 1995; **333**: 1232–1235.
12 Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K *et al.* Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr* 2005; **24**: 466–477.
13 Kehlet H. Fast-track colorectal surgery. *Lancet* 2008; **371**: 791–793.
14 Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. *Ann Surg* 2007; **245**: 867–872.
15 Wind J, Polle SW, Fung Kon Jin PH, Dejong CH, von Meyenfeldt MF, Ubbink DT *et al.* Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg* 2006; **93**: 800–809.
16 Prytherch DR, Whiteley MS, Higgins B, Weaver PC, Prout WG, Powell SJ. POSSUM and Portsmouth POSSUM for predicting mortality. Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. *Br J Surg* 1998; **85**: 1217–1220.
17 Maessen J, Dejong CH, Hausel J, Nygren J, Lassen K, Andersen J *et al.* A protocol is not enough to implement an enhanced recovery programme for colorectal resection. *Br J Surg* 2007; **94**: 224–231.
18 Nygren J, Hausel J, Kehlet H, Revhaug A, Lassen K, Dejong C *et al.* A comparison in five European Centres of case mix, clinical management and outcomes following either conventional or fast-track perioperative care in colorectal surgery. *Clin Nutr* 2005; **24**: 455–461.
19 Lang M, Niskanen M, Miettinen P, Alhava E, Takala J. Outcome and resource utilization in gastroenterological surgery. *Br J Surg* 2001; **88**: 1006–1014.
20 Basse L, Thorbøl JE, Løssl K, Kehlet H. Colonic surgery with accelerated rehabilitation or conventional care. *Dis Colon Rectum* 2004; **47**: 271–277.
21 Braga M, Vignali A, Gianotti L, Zuliani W, Radaelli G, Gruarin P *et al.* Laparoscopic *versus* open colorectal surgery: a randomized trial on short-term outcome. *Ann Surg* 2002; **236**: 759–766.
22 Alves A, Panis Y, Mathieu P, Mantion G, Kwiatkowski F, Slim K. Postoperative mortality and morbidity in French patients undergoing colorectal surgery: results of a prospective multicenter study. *Arch Surg* 2005; **140**: 278–283.
23 Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM *et al.* Short-term endpoints of conventional *versus* laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005; **365**: 1718–1726.
24 Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ *et al.* Laparoscopic surgery *versus* open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005; **6**: 477–484.
25 Basse L, Hjort Jakobsen D, Billesbølle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg* 2000; **232**: 51–57.
26 Ong ES, Alassas M, Dunn KB, Rajput A. Colorectal cancer surgery in the elderly: acceptable morbidity? *Am J Surg* 2008; **195**: 344–348.
27 Heriot AG, Tekkis PP, Smith JJ, Cohen CR, Montgomery A, Audisio RA *et al.* Prediction of postoperative mortality in elderly patients with colorectal cancer. *Dis Colon Rectum* 2006; **49**: 816–824.
28 Tekkis PP, Poloniecki JD, Thompson MR, Stamatakis JD. Operative mortality in colorectal cancer: prospective national study. *BMJ* 2003; **327**: 1196–1201.
29 Alley PG. Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group. *Lancet* 2000; **356**: 968–974.
30 Manku K, Bacchetti P, Leung JM. Prognostic significance of postoperative in-hospital complications in elderly patients. I. Long-term survival. *Anesth Analg* 2003; **96**: 583–589.
31 Smith JJ, Lee J, Burke C, Contractor KB, Dawson PM. Major colorectal cancer resection should not be denied to the elderly. *Eur J Surg Oncol* 2002; **28**: 661–666.
32 Maessen J, Dejong C, Kessels AG, von Meyenfeldt MF, Enhanced Recovery After Surgery (ERAS) Group. Length of stay: an inappropriate readout of the success of enhanced recovery programs. *World J Surg* 2008; **32**: 971–975.
33 National Institute for Health and Clinical Excellence. Nutritional support in adults: oral supplements, enteral tube feeding and parenteral nutrition. 2006; http://www.nice.org.uk/nicemedia/pdf/cg032fullguideline.pdf [accessed 1 July 2008].
34 Murphy PM, Modi P, Rahamim J, Wheatley T, Lewis SJ. An investigation into the current peri-operative nutritional management of oesophageal carcinoma patients in major carcinoma centres in England. *Ann R Coll Surg Engl* 2006; **88**: 358–362.
35 Soop M, Carlson GL, Hopkinson J, Clarke S, Thorell A, Nygren J *et al.* Randomized clinical trial of the effects of immediate enteral nutrition on metabolic responses to major colorectal surgery in an enhanced recovery protocol. *Br J Surg* 2004; **91**: 1138–1145.
36 Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P *et al.* ESPEN Guidelines on Enteral Nutrition: surgery including organ transplantation. *Clin Nutr* 2006; **25**: 224–244.
37 Malnutrition Advisory Group. Malnutrition Universal Screening Tool. British Association for Parenteral and Enteral Nutrition: Redditch. http://www.bapen.org.uk/must_tool.html [accessed 1 July 2008].
38 Bowles TA, Sanders KM, Colson M, Watters DA. Simplified risk stratification in elective colorectal surgery. *ANZ J Surg* 2008; **78**: 24–27.

39 Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002; **183**: 630–641.
40 Salerno G, Daniels IR, Brown G, Heald RJ, Moran BJ. Magnetic resonance imaging pelvimetry in 186 patients with rectal cancer confirms an overlap in pelvic size between males and females. *Colorectal Dis* 2006; **8**: 772–776.
41 Slim K, Vicaut E, Panis Y, Chipponi J. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. *Br J Surg* 2004; **91**: 1125–1130.

## Colon lipoma mimicking appendicitis

A 62-year-old patient was admitted with suspected appendicitis. On the preoperative CT scan, a 4 × 6 × 8 cm lipoma was found with suspicion of invagination of part of the ileum. A right hemicolectomy was done; the lipoma was ulcerated at the apex which explained the symptoms. The patient had an uneventful recovery and was discharged on the 5th postoperative day.

Sadowski-Cron C, Tharakan S, Muff B.: Department of General Surgery, Spital Bülach, CH - 8180 Bülach, Switzerland (e-mail: ch.sadowski@bluewin.ch)

**Snapshots in Surgery: to view submission guidelines, submit your snapshot and view the archive, please visit www.bjs.co.uk**

Clinical Nutrition 28 (2009) 636–641

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original Article

# Gastric emptying of three liquid oral preoperative metabolic preconditioning regimens measured by magnetic resonance imaging in healthy adult volunteers: A randomised double-blind, crossover study

Dileep N. Lobo [a,*], Paul O. Hendry [b], Gabriel Rodrigues [a], Luca Marciani [c], John J. Totman [d], Jeff W. Wright [a], Tom Preston [e], Penny Gowland [f], Robin C. Spiller [c], Kenneth C.H. Fearon [b]

[a] Division of Gastrointestinal Surgery, Nottingham Digestive Diseases Centre Biomedical Research Unit, Nottingham University Hospitals, Queen's Medical Centre, Nottingham, UK
[b] Department of Surgery, Edinburgh Royal Infirmary, Edinburgh, UK
[c] Division of Gastroenterology, Nottingham Digestive Diseases Centre Biomedical Research Unit, Nottingham University Hospitals, Queen's Medical Centre, Nottingham, UK
[d] Brain & Body Centre, University of Nottingham, University Park, Nottingham, UK
[e] Scottish Universities Environmental Research Centre, East Kilbride, UK
[f] Sir Peter Mansfield Magnetic Resonance Centre, University of Nottingham, University Park, Nottingham, UK

ARTICLE INFO

*Article history:*
Received 8 December 2008
Accepted 2 May 2009

*Keywords:*
Gastric emptying time
Magnetic resonance imaging
Clear liquids
Suspensions
Preoperative fasting
Randomised controlled study
Volunteer study

SUMMARY

*Background & aims:* Preoperative starvation has many undesirable effects but the minimum length of fasting is limited by gastric emptying, which may be dependent on nutrient content, viscosity and osmolarity of the feed. We compared the gastric emptying of two types of preoperative metabolic preconditioning drinks [Oral Nutritional Supplement (ONS) (Fresenius Kabi, Germany) and preOp® (Nutricia Clinical Care, UK)] in healthy volunteers.

*Methods:* Twenty (10 male, 10 female) healthy adult volunteers were studied on 3 separate occasions in a randomised crossover manner. Volunteers ingested 400 ml preOp®, which is a clear carbohydrate drink (CCD) (50 g carbohydrate, 0 g protein), 70 g ONS (50 g carbohydrate and 15 g glutamine) dissolved in water to a total volume of 400 ml (ONS400) and 300 ml (ONS300). Gastric emptying time was measured using magnetic resonance imaging.

*Results:* Mean (95% CI) $T_{50}$ and $T_{100}$ gastric emptying times for CCD were significantly lower ($p < 0.001$) compared with ONS400 and ONS300. $T_{50}$ was 47 (39–55), 78 (69–87) and 81 (70–92) min for CCD, ONS400 and ONS300 respectively. Correspondingly $T_{100}$ was 94 (79–110), 156 (138–173) and 162 (140–184) min. Residual gastric volumes returned to baseline 120 min after CCD and 180 min after ONS400 and ONS300.

*Conclusions:* The faster gastric emptying for CCD compared to ONS400 and ONS300 signifies that gastric emptying may be more dependent on nutrient load than volume or viscosity in healthy volunteers. While it is safe to give CCD 2 h preoperatively, ONS400 and ONS300 should be given at least 3 h preoperatively.



## 1. Introduction

Modern perioperative care, in particular the introduction of Enhanced Recovery After Surgery programmes, has dramatically improved the speed of postoperative recovery and reduced postoperative morbidity.[1] Within these programmes patients are no longer starved for 12 h prior to major surgery but instead follow current anaesthetic guidelines which recommend intake of clear fluids up until two hours before initiation of anaesthesia and a six hour fast for solid food.[2–4] As part of current fasting guidelines, preoperative metabolic conditioning with 400 ml of a clear carbohydrate drink (CCD) two hours before the induction of anaesthesia has been shown to reduce postoperative insulin resistance, postoperative nausea and vomiting and preoperative discomfort and anxiety, and improve patient well-being.[5–8] This volume of CCD empties completely from the stomach within 90 min and does not

* Corresponding author at: Division of Gastrointestinal Surgery, Nottingham University Hospitals, Queen's Medical Centre, Nottingham NG7 2UH, UK. Tel.: +44 115 8231149; fax: +44 115 8231160.
*E-mail address:* dileep.lobo@nottingham.ac.uk (D.N. Lobo).

0261-5614/$ – see front matter © 2009 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.
doi:10.1016/j.clnu.2009.05.002

increase aspiration risk during induction of anaesthesia.[5] One currently available CCD, [Nutricia preOp® (Nutricia Clinical Care, Trowbridge, UK)], has already been shown to be safe in a large number of patients undergoing major abdominal surgery.[5,9–12]

The use of additional metabolic conditioning agents such as glutamine and antioxidants may be of potential benefit to patients undergoing major abdominal surgery. Glutamine is a conditionally essential amino acid, which improves both gastrointestinal perfusion and immune function.[13] Antioxidant supplementation has been demonstrated to improve morbidity and survival in critically ill patients.[14] A new product containing glutamine and antioxidants in addition to carbohydrate [Oral Nutrition Supplement (ONS), Fresenius Kabi, Bad Homburg, Germany] may, therefore, provide additional benefits, beyond carbohydrate loading alone, to surgical patients. The time taken for ONS to empty from the stomach and, therefore, the safe time frame for preoperative administration, is not known. Gastric emptying is affected primarily by nutrient content, although volume, viscosity[15] and osmolality of the feed[16] also play a part. It is, therefore, important to control for these aspects.

Measurements of gastric emptying have been employed to study gastrointestinal function in a number of conditions, but results may differ according to the methodology.[17,18] Scintigraphic techniques were regarded as the gold standard for such studies, but magnetic resonance imaging (MRI) is now becoming established rapidly as the benchmark test as it provides a direct measure of gastric volume in real time.[19–22]

In this study we compared the gastric emptying time, using MRI, of two different types of preoperative metabolic conditioning regimes [ONS and CCD (preOp®)] in healthy volunteers. As the gastric emptying of 400 ml CCD has been determined previously using scintigraphy,[5] we compared identical volumes (400 ml) of the two drinks with the recommended dose of administration of ONS (300 ml).

## 2. Subjects and methods

### 2.1. Study design, setting and ethics

The protocol for this randomised, double-blind, three-way crossover study on healthy adult volunteers was approved by the University of Nottingham Medical School Research Ethics Committee (approval K/5/2007) and informed written consent was obtained from all volunteers prior to enrolment. The study was carried out according to the principles of the Declaration of Helsinki of the World Medical Association (http://wma.net). A system to report adverse events was in place.

### 2.2. Subjects

We studied 20 healthy adult volunteers (10 male and 10 female, aged 18–45 years), suitable for MRI scanning (e.g. no metal implants in the body), with a normal body mass index (20–26 kg/m$^2$) and with no history of abdominal surgery or gastrointestinal disorders. Female volunteers were included only if they were not pregnant. A medical questionnaire was administered and a clinical examination performed prior to recruitment. Any volunteer who wished to withdraw from the study was entitled to do so at any time without giving a reason.

### 2.3. Interventions

Each volunteer was randomised in a crossover manner to ingest 400 ml preOp® (50 g carbohydrate, 0 g protein) (CCD), 70 g ONS (50 g carbohydrate and 15 g glutamine) dissolved in water to a total volume of 400 ml (ONS400) and 70 g ONS dissolved in 250 ml water to a total volume of 300 ml (ONS300). Volunteers reported for the studies at 0830 h after an overnight fast, on three separate occasions, each 7 days apart. They were instructed to abstain from alcohol and medications for 24 h, and caffeine and strenuous exercise for 18 h. Baseline measurements included height, weight, body mass index and a fasting MRI scan.

The constituents and physical properties of the three test drinks are listed in Table 1. The drinks were reconstituted on the morning of each study and placed into identical opaque plastic bottles by a person not involved in the study. Volunteers were asked to ingest the drink from the bottle within 5 min and time zero was defined as the end of ingestion of the drink.

### 2.4. Magnetic resonance imaging (MRI)

MRI scanning was performed on a 1.5 T Philips Achieva scanner (Philips Healthcare, Eindhoven, The Netherlands) at the University of Nottingham. Each volunteer was positioned supine in the scanner with a sensitivity encoding (SENSE) body coil wrapped around the abdomen. First, a coarse scout scan was taken to locate

**Table 1**
Composition of the drinks.

| | CCD – clear carbohydrate drink (400 ml Nutricia preOp®) | ONS400 [70 g Oral Nutrition Supplement (ONS) dissolved in water to a total volume of 400 ml] | ONS300 [70 g Oral Nutrition Supplement (ONS) dissolved in 250 ml water to a total volume of 300 ml] |
|---|---|---|---|
| Carbohydrate | | | |
| Maltodextrin + saccharose + modified starch + gum arabic | – | 50 g | 50 g |
| Maltodextrin + fructose | 50.4 g | – | – |
| Glutamine | – | 15 g | 15 g |
| Vitamin C | – | 750 mg | 750 mg |
| Vitamin E | – | 250 mg | 250 mg |
| Green tea extract | – | 1 g | 1 g |
| β carotene | – | 5 mg | 5 mg |
| Zinc | – | 10 mg | 10 mg |
| Selenium | – | 150 μg | 150 μg |
| Energy | 200 kcal (836 kJ) | 234 kcal (978 kJ) | 234 kcal (978 kJ) |
| Dry matter content | 11.3% | 16.3% | 21.8% |
| pH | 4.9 | 3.9 | 3.9 |
| Density | 1.049 g/ml | 1.06 g/ml | 1.079 g/ml |
| Viscosity [at $\gamma = 1$ (1/s)] | 2.30 mPa | 180 mPa | 627 mPa |
| Osmolarity | 228 mOsm/kg | 508 mOsm/kg | 698 mOsm/kg |

the position of the abdominal organs and plan the position of the image planes followed by a calibration scan allowing automatic setup of the scanner specific to the volunteer.

For the gastric emptying a balanced turbo field echo (BTFE) imaging sequence was used to acquire 40 transverse (perpendicular to the longitudinal axis of the body) images with acquired planar resolutions of 2.50 mm × 1.56 mm (reconstructed to 1.56 mm × 1.56 mm) and slice thickness of 10 mm. This BTFE sequence (TR = 2.4 ms, TE = 1.19 ms, flip angle 45°) visualises fluid containing structures (hydrated test meals) with bright contrast against the surrounding organs. Each image set was acquired during a breath-hold of 17.6 s. MRI scans were performed in the fasted state (baseline), immediately after ingesting the drink (time 0), and then at 20 min intervals until the stomach was empty.

The data set from each time point was recalled on a UNIX workstation and viewed to locate the gastric lumen and its contents. An example of a series through the abdomen of one subject is shown in Fig. 1. On such transverse sections, Analyze 6 (Biomedical Imaging Resources, Mayo Clinic, Rochester, MN) was used to trace manually around the region of interest (ROI) of the gastric contents on each slice. After this the volume of the gastric contents at each time point was calculated by summing across all ROIs. The totals for each time point were then tabulated and plotted onto spreadsheets in Microsoft® Excel (Microsoft® Corporation) to determine the gastric emptying kinetics. Individual gastric emptying curves were fitted on Microsoft® Excel to calculate the gastric half emptying time, $T_{50}$. The curves were then extrapolated to baseline in a linear manner to calculate $T_{100}$. The volume remaining in the stomach at $t = 60$, 120 and 180 min were also measured using MRI.

### 2.5. End points and sample size

The primary end point of the study was time to half gastric emptying ($T_{50}$) of the three test drinks as measured by MRI. Secondary end points included $T_{100}$ gastric emptying time and residual gastric volumes at 60, 120 and 180 min. Based on pilot scans, we anticipated a mean difference in $T_{50}$ gastric emptying time of 30 min with a standard deviation of 30 min between CCD and ONS400. Assuming an $\alpha$ error of 0.01 and a power of 90%, the sample size was calculated to be 18. We recruited 20 subjects, making allowance for a 10% drop out rate.

### 2.6. Randomisation and blinding

The order of administration of the three test drinks was determined using a web-based random number generator (http://www.randomizer.org/). Allocations were then concealed in sequentially numbered sealed opaque envelopes in triplicate, and were opened before each leg of the study by a person not involved in the study. That person then reconstituted the drinks, transferred them to opaque bottles and handed them to the investigators. Both the subjects and the investigators were blinded to group allocation. The randomisation code was broken after completion of the statistical analysis.

### 2.7. Statistical analysis

As the data were distributed normally, all results were expressed as mean (95% CI) or mean (SE). Differences between groups were tested for significance using the Student $t$-test (paired and unpaired), and were considered significant at $P < 0.05$. Statistical analysis was performed using SPSS for Windows® v 16.0 (SPSS Inc., Chicago, IL, USA) and graphs were plotted on Microsoft® Excel.

### 2.8. Role of sponsors of the study

This was an investigator initiated study and the sponsors did not have any role in the study design, data collection, analysis and interpretation, writing of the paper or in the decision to submit the paper for publication.

## 3. Results

The mean (SE) age, weight, height and body mass index (BMI) of the 20 volunteers were 29.4 (1.7) years, 68.1 (2.1) kg, 1.70 (0.02) m and 23.4 (0.4) km/m$^2$ respectively. Corresponding values for the 10 male volunteers were 33.0 (2.5) years, 75.3 (2.3) kg, 1.74 (0.03) m

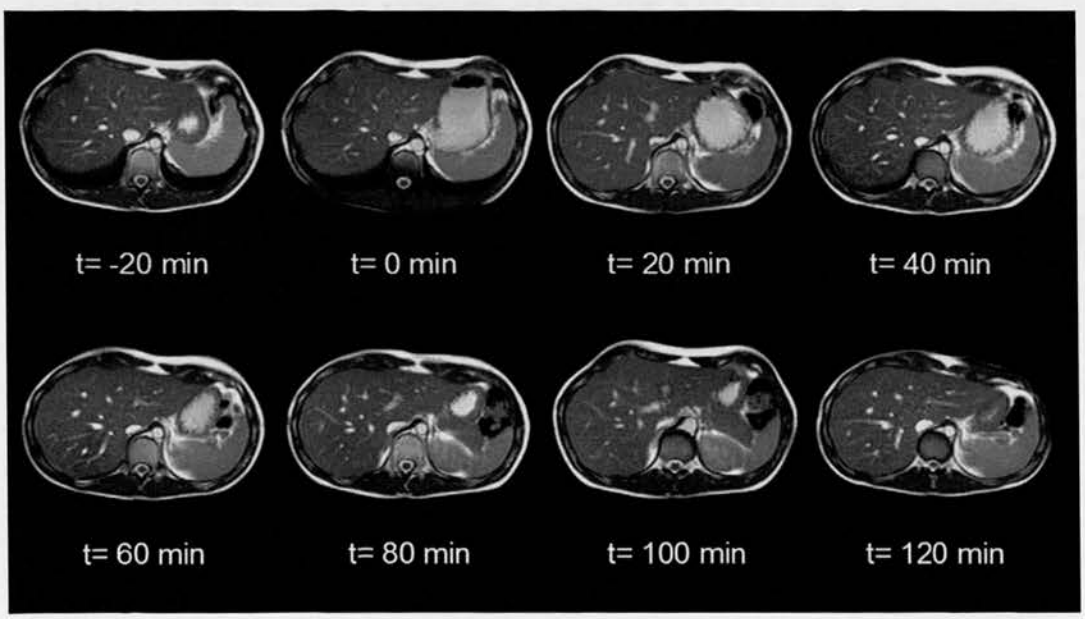



**Fig. 1.** Sequential axial MRI scans in one subject before and after ingestion of the drink.

**Table 2**
Residual fasting gastric volume.

| | All subjects ($n = 20$) | Male subjects ($n = 10$) | Female subjects ($n = 10$) |
|---|---|---|---|
| Before CCD (400 ml Nutricia preOp®) | 21 (12–30) | 21 (6–35) | 21 (7–35) |
| Before ONS400 [70 g Oral Nutrition Solution (ONS) dissolved in water to a total volume of 400 ml] | 29 (17–41) | 27 (7–47) | 31 (12–49) |
| Before ONS300 [70 g Oral Nutrition Solution (ONS) dissolved in 250 ml water to a total volume of 300 ml] | 32 (22–42) | 34 (23–46) | 30 (11–49) |
| Total | 27 (21–33) | 28 (19–36) | 27 (18–36) |

All values are mean (95% CI) ml. None of the differences were statistically significant.

and 24.7 (0.3) km/m$^2$ and for the 10 female volunteers 25.8 (2.0) years, 60.8 (1.4) kg, 1.66 (0.02) m and 22.1 (0.6) km/m$^2$. All subjects completed the three arms of the study and none had to be withdrawn. One subject experienced mild nausea after ingesting ONS300, but there were no other side effects. Residual gastric volume, as measured by MRI, after an overnight fast, ranged from 0 to 95 ml (Table 2). Mean (95% CI) $T_{50}$ gastric emptying times were significantly lower ($p < 0.001$) with CCD, being 47 (39–55) min compared with 78 (69–87) and 81 (70–92) min for ONS400 and ONS300 respectively. Corresponding $T_{100}$ times were 94 (79–110), 156 (138–173) and 162 (140–184) min (Figs. 2 and 3). Although $T_{50}$ and $T_{100}$ gastric emptying times were 11–14 min and 22–28 min respectively longer in females than males, these differences were not statistically significant. The residual gastric volumes at 60, 120 and 180 min are shown in Fig. 4. At 120 min, the residual volume for CCD was equivalent to the fasting residual volume ($p = 0.84$), while this volume was significantly greater than the fasting residual volume for ONS400 ($p < 0.001$) and ONS300 ($p = 0.004$). The residual volume for ONS400 and ONS300 had returned to baseline by 180 min.

## 4. Discussion

This study has confirmed earlier work that a clear liquid containing carbohydrate but no protein or fat completely empties from the stomach in about 90 min[5] and, therefore, further supports the evidence base for the guidelines that patients can have clear fluids containing carbohydrates up to 2 h before the induction of anaesthesia.[2–4,6] However, equally, it has been demonstrated that it may not be safe to let patients have a liquid suspension containing carbohydrate and amino acids 2 h prior to anaesthesia and that a safe duration for ingesting such liquids is 3–4 h preoperatively.

Even after an overnight fast, the stomach is never completely empty and using direct measurements of gastric content volume, we have shown that the residual volume in healthy volunteers can range from 0 to 95 ml with a mean of 27 ml. Fasting residual gastric volumes were not significantly different when males and females were compared. CCD, which is a clear solution that contains no fat or protein, emptied at a significantly quicker rate than ONS400 and ONS300, which were suspensions. Despite there being a difference in volume, osmolarity, viscosity and density, the rates of emptying of drinks ONS400 and ONS300 were similar. These findings suggest that the gastric emptying of liquids is more dependent on the presence of particulate matter and the nutrient content rather than general physical properties such as volume, osmolarity, viscosity and density.

The rate of gastric emptying was slower in female subjects than in males for all three test drinks, although statistical significance was not reached due to the relatively small sample size. These gender differences have been described previously[23–25] and may be due to the relaxational effect of female sex hormones, especially progesterone, on gastric smooth muscle.[23,24] However, given the relatively small differences in gastric emptying times, it is uncertain whether these gender differencess are clinically relevant.

Although measurements of gastric emptying time using MRI have been validated with scintigraphic techniques,[21] and our study has shown that the emptying of CCD using MRI was very similar to the results obtained with the same drink by Nygren et al.[5] using scintigraphy, it should be mentioned that the measurements made

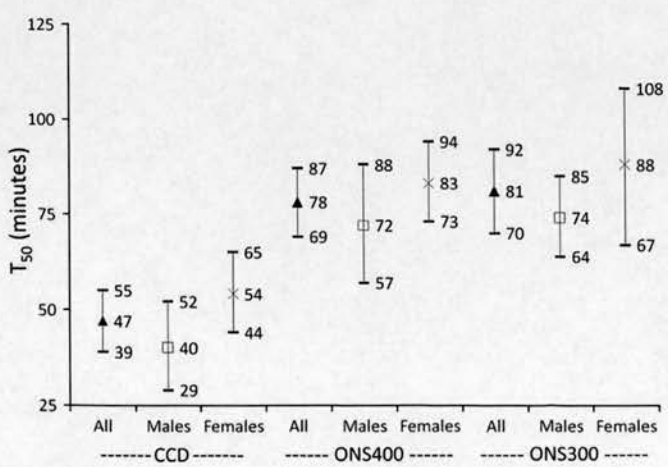



**Fig. 2.** $T_{50}$ gastric emptying time. All values are mean (95% CI) minutes. For all subjects, ONS400 vs. ONS300 not significant; CCD vs. ONS400 and CCD vs. ONS300, $p < 0.001$. Differences between males and females for each drink were not significant. CCD – clear carbohydrate drink: 400 ml Nutricia preOp®, ONS400: 70 g Oral Nutrition Supplement (ONS) dissolved in water to a total volume of 400 ml, ONS300: 70 g Oral Nutrition Supplement (ONS) dissolved in 250 ml water to a total volume of 300 ml.

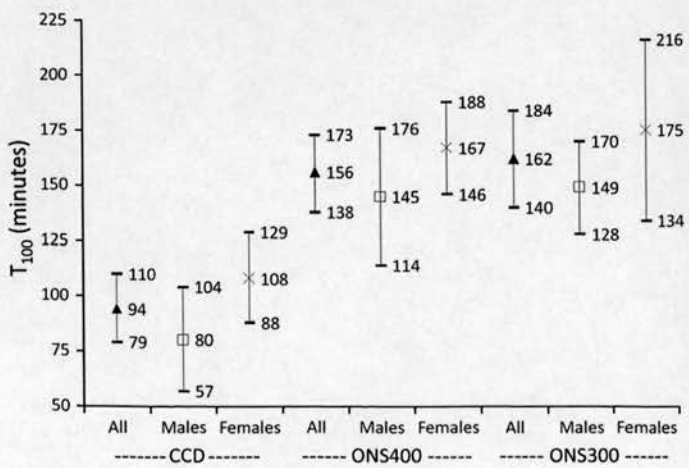



**Fig. 3.** $T_{100}$ gastric emptying time. All values are mean (95% CI) minutes. For all subjects, ONS400 vs. ONS300 not significant; CCD vs. ONS400 and CCD vs. ONS300, $p < 0.001$. Differences between males and females for each drink were not significant. CCD – clear carbohydrate drink: 400 ml Nutricia preOp®, ONS400: 70 g Oral Nutrition Supplement (ONS) dissolved in water to a total volume of 400 ml, ONS300: 70 g Oral Nutrition Supplement (ONS) dissolved in 250 ml water to a total volume of 300 ml.

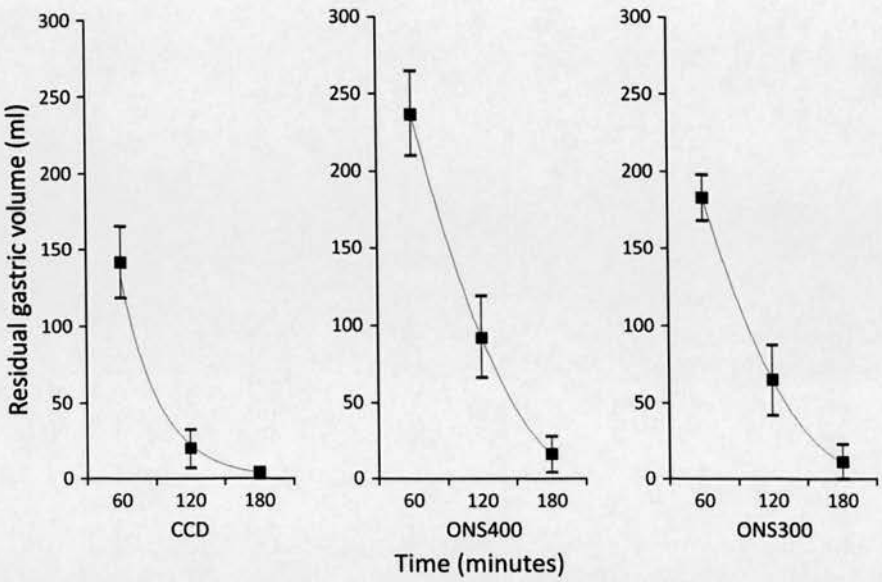



**Fig. 4.** Residual gastric volume at 60, 120 and 180 min. All values are mean (95% CI) ml. *P*-values for all subjects: 60 min – CCD vs. ONS400 < 0.001, CCD vs. ONS300 = 0.006, ONS400 vs. ONS300 < 0.001; 120 min – CCD vs. ONS400 < 0.001, CCD vs. ONS300 < 0.001, ONS400 vs. ONS300 = 0.037; 180 min – CCD vs. ONS400 = 0.025, CCD vs. ONS300 = 0.25 (NS), ONS400 vs. ONS300 = 0.55 (NS). Differences between males and females for each time point were not significant. CCD – clear carbohydrate drink: 400 ml Nutricia preOp®, ONS400: 70 g Oral Nutrition Supplement (ONS) dissolved in water to a total volume of 400 ml, ONS300: 70 g Oral Nutrition Supplement (ONS) dissolved in 250 ml water to a total volume of 300 ml.

by the two techniques are, in fact, slightly different. Scintigraphy measures the residual isotope in the stomach and not the volume of the contents. On the other hand, MRI measures the actual volume of the gastric contents and this is usually a sum of the volume of the drink administered and the volume of the gastric secretions. The intragastric volume measured by MRI may, therefore, be increased by feeds that increase gastric secretion significantly. Amino acids stimulate gastrin release[26] and, hence, gastric secretion[27] and thus may increase intragastric volumes and lead to a delay in decline in gastric volumes postprandially.

The gastric residual volume had returned to the fasting baseline within 120 min of ingesting CCD, once again confirming that it is safe to administer such clear liquids up to 2 h prior to the induction of anaesthesia. However, for ONS400 and ONS300 the mean residual gastric volumes at 120 min were 3.4 and 2.4 times the baseline, suggesting that a 2 h preoperative fast after ingesting these drinks may not be adequate. However, at 180 min the residual gastric volumes had returned to baseline for both ONS400 and ONS300, indicating that this duration of preoperative fasting may be safe when these drinks are administered. It has been argued that patients have a certain degree of anxiety in the preoperative period and that this may prolong gastric emptying time, thereby suggesting that data obtained from healthy volunteers on gastric emptying time should be extrapolated to preoperative patients with caution. However, it has been shown that preoperative anxiety has no effect on gastric emptying time.[5] Morbidly obese patients have also been shown to have gastric emptying patterns that are similar to those of lean patients.[28,29] Diabetic patients with autonomic neuropathy can have delayed gastric emptying, possibly increasing the risk of regurgitation and aspiration,[30] and results obtained from healthy subjects are not applicable to this group of patients. However, some patients with uncomplicated type-2 diabetes can have normal gastric emptying and a study on preoperative carbohydrate loading did not find an increased aspiration rate in type-2 diabetic patients.[10] We can, therefore, recommend that unless significant comorbidity is present, the period of preoperative fasting after ingestion of 300–400 ml of a liquid suspension should be between 3 and 4 h. This guidance is in addition to the standard guidelines issued by several National Anaesthesia Societies recommending intake of clear fluids up until 2 h before induction of anaesthesia and a 6 h fast for solid food.[2–4]

It has been proposed that patients should be in a metabolically fed state rather than fasted when they go to theatre. This can be achieved by provision of a CCD before midnight and 2–3 h before surgery. This treatment decreases preoperative thirst, hunger and anxiety[5–7] and reduces postoperative insulin resistance significantly.[8] It also results in patients being in a more anabolic state with less postoperative nitrogen and protein losses,[31,32] and better maintained lean body mass[11] and muscle strength.[33] Data from a randomised trial suggests that preoperative carbohydrate loading in patients undergoing colorectal surgery results in a shorter length of hospital stay.[9] Although ONS400 and ONS300 may have the added advantage of improving gastrointestinal perfusion and antioxidant defences, further studies looking at pharmacokinetic profiles, effects on insulin sensitivity, clinical safety and clinical efficacy have to be undertaken before general use can be recommended.

## Conflict of interest

DNL and KCHF have received research grants, speakers' honoraria and travel bursaries from Fresenius Kabi, Bad Homburg, Germany. DNL has also received funding from Nutricia Clinical Care, UK for unrelated work. POH has received a speaker's honorarium and travel bursary from Nutricia Clinical Care, UK. None of the other authors has a conflict of interest to declare.

## Acknowledgements

*Funding*: This study was funded by an unrestricted grant from Fresenius Kabi, Bad Homburg, Germany through the Enhanced Recovery After Surgery (ERAS) group. GR was a recipient of the Dr. Prem Nath Berry Educational Trust Scholarship from the Indian High Commission in London.

## Appendix. Author contributions

DNL: Study design, obtaining funding, statistical analysis, data interpretation, writing of the manuscript, critical revision and final approval.

POH: Study design, data collection and analysis, writing of the manuscript and final approval.

GR: Study design, data collection and analysis, writing of the manuscript and final approval.

LM: Study design, data collection, analysis and interpretation, writing of the manuscript, critical revision and final approval.

JJT: Data collection and analysis, writing of the manuscript and final approval.

JWW: Study design, data collection and interpretation, writing of the manuscript, critical revision and final approval.

TP: Study design, data interpretation, critical revision and final approval of the manuscript.

PG: Study design, data interpretation, critical revision and final approval of the manuscript.

RCS: Study design, data interpretation, writing of the manuscript, critical revision and final approval.

KCHF: Study design, obtaining funding, data interpretation, writing of the manuscript, critical revision and final approval.

## References


1. Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr* 2005;**24**:466–77.
2. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: a report by the American Society of Anesthesiologist Task Force on Preoperative Fasting. *Anesthesiology* 1999;**90**:896–905.
3. Soreide E, Ljungqvist O. Modern preoperative fasting guidelines: a summary of the present recommendations and remaining questions. *Best Pract Res Clin Anaesthesiol* 2006;**20**:483–91.
4. Woods DM, Macpherson R. Australian and New Zealand guidelines for preoperative fasting. *Anaesth Intensive Care* 2007;**35**:622–3.
5. Nygren J, Thorell A, Jacobsson H, Larsson S, Schnell PO, Hylen L, et al. Preoperative gastric emptying. Effects of anxiety and oral carbohydrate administration. *Ann Surg* 1995;**222**:728–34.
6. Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications. *Cochrane Database Syst Rev*; 2003::CD004423.
7. Hausel J, Nygren J, Lagerkranser M, Hellström PM, Hammarqvist F, Almström C, et al. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesth Analg* 2001;**93**:1344–50.
8. Nygren J. The metabolic effects of fasting and surgery. *Best Pract Res Clin Anaesthesiol* 2006;**20**:429–38.
9. Noblett SE, Watson DS, Huong H, Davison B, Hainsworth PJ, Horgan AF. Preoperative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. *Colorectal Dis* 2006;**8**:563–9.
10. Breuer JP, von Dossow V, von Heymann C, Griesbach M, von Schickfus M, Mackh E, et al. Preoperative oral carbohydrate administration to ASA III-IV patients undergoing elective cardiac surgery. *Anesth Analg* 2006;**103**:1099–108.
11. Yuill KA, Richardson RA, Davidson HI, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively – a randomised clinical trial. *Clin Nutr* 2005;**24**:32–7.
12. Hendry PO, Balfour A, Potter MA, Mander BJ, Bartolo DC, Anderson DN, et al. Preoperative conditioning with oral carbohydrate loading and oral nutritional supplements can be combined with mechanical bowel preparation prior to elective colorectal resection. *Colorectal Dis* 2008;**10**:907–10.
13. Roth E. Nonnutritive effects of glutamine. *J Nutr* 2008;**138**:2025S–31S.
14. Berger MM, Chiolero RL. Antioxidant supplementation in sepsis and systemic inflammatory response syndrome. *Crit Care Med* 2007;**35**:S584–90.
15. Marciani L, Gowland PA, Spiller RC, Manoj P, Moore RJ, Young P, et al. Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI. *Am J Physiol Gastrointest Liver Physiol* 2001;**280**:G1227–33.
16. Horowitz M, Dent J, Fraser R, Sun W, Hebbard G. Role and integration of mechanisms controlling gastric emptying. *Dig Dis Sci* 1994;**39**:7S–13S.
17. Bratten J, Jones MP. New directions in the assessment of gastric function: clinical applications of physiologic measurements. *Dig Dis* 2006;**24**:252–9.
18. Lin HC, Prather C, Fisher RS, Meyer JH, Summers RW, Pimentel M, et al. AMS Task Force Committee on Gastrointestinal Transit. Measurement of gastrointestinal transit. *Dig Dis Sci* 2005;**50**:989–1004.
19. Schwizer W, Maecke H, Fried M. Measurement of gastric emptying by magnetic resonance imaging in humans. *Gastroenterology* 1992;**103**:369–76.
20. Boulby P, Gowland P, Adams V, Spiller RC. Use of echo planar imaging to demonstrate the effect of posture on the intragastric distribution and emptying of an oil/water meal. *Neurogastroenterol Motil* 1997;**9**:41–7.
21. Feinle C, Kunz P, Boesiger P, Fried M, Schwizer W. Scintigraphic validation of a magnetic resonance imaging method to study gastric emptying of a solid meal in humans. *Gut* 1999;**44**:106–11.
22. Wright J, Evans D, Gowland P, Mansfield P. Validation of antroduodenal motility measurements made by echo-planar magnetic resonance imaging. *Neurogastroenterol Motil* 1999;**11**:19–25.
23. Datz FL, Christian PE, Moore J. Gender-related differences in gastric emptying. *J Nucl Med* 1987;**28**:1204–7.
24. Degen LP, Phillips SF. Variability of gastrointestinal transit in healthy women and men. *Gut* 1996;**39**:299–305.
25. Lobo DN, Bostock KA, Bush D, Macdonald IA, Perkins AC, Neal KR, et al. Reproducibility and normal ranges for gastric emptying in normal volunteers using a test meal designed for post-operative patients. *Nucl Med Commun* 2002;**23**:97–101.
26. Taylor IL, Byrne WJ, Christie DL, Ament ME, Walsh JH. Effect of individual L-amino acids on gastric acid secretion and serum gastrin and pancreatic polypeptide release in humans. *Gastroenterology* 1982;**83**:273–8.
27. Kidd M, Modlin IM, Tang LH. Gastrin and the enterochromaffin-like cell: an acid update. *Dig Surg* 1998;**15**:209–17.
28. Maltby JR, Pytka S, Watson NC, Cowan RA, Fick GH. Drinking 300 ml of clear fluid two hours before surgery has no effect on gastric fluid volume and pH in fasting and non-fasting obese patients. *Can J Anaesth* 2004;**51**:111–5.
29. Harter RL, Kelly WB, Kramer MG, Perez CE, Dzwonczyk RR. A comparison of the volume and pH of gastric contents of obese and lean surgical patients. *Anesth Analg* 1998;**86**:147–52.
30. Kong MF, Horowitz M. Diabetic gastroparesis. *Diabet Med* 2005;**22**(Suppl. 4): 13–8.
31. Crowe PJ, Dennison A, Royle GT. The effect of pre-operative glucose loading on postoperative nitrogen metabolism. *Br J Surg* 1984;**71**:635–7.
32. Svanfeldt M, Thorell A, Hausel J, Soop M, Rooyackers O, Nygren J, et al. Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics. *Br J Surg* 2007;**94**:1342–50.
33. Henriksen MG, Hessov I, Dela F, Hansen HV, Haraldsted V, Rodt SA. Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery. *Acta Anaesthesiol Scand* 2003;**47**:191–9.

Randomized clinical trial

# Randomized clinical trial of laxatives and oral nutritional supplements within an enhanced recovery after surgery protocol following liver resection

**P. O. Hendry[1], R. M. van Dam[4], S. F. F. W. Bukkems[4], D. W. McKeown[2], R. W. Parks[1], T. Preston[3], C. H. C. Dejong[4], O. J. Garden[1] and K. C. H. Fearon[1] on behalf of the Enhanced Recovery After Surgery (ERAS) Group**

[1]Clinical and Surgical Sciences (Surgery) and [2]Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary, Edinburgh, and [3]Scottish Universities Environmental Research Centre, East Kilbride, UK, and [4]Maastricht University Medical Centre and NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University, The Netherlands

*Correspondence to:* Mr P. O. Hendry, Clinical and Surgical Sciences (Surgery), Royal Infirmary, 51 Little France Crescent, Edinburgh EH16 4SA, UK (e-mail: paul.hendry@ed.ac.uk)

**Background:** **Routine laxatives may expedite gastrointestinal recovery and early tolerance of food within an enhanced recovery after surgery (ERAS) programme. Combined with carbohydrate loading and oral nutritional supplements (ONS), it may further enhance recovery of gastrointestinal function and promote earlier overall recovery.**

**Methods:** **Seventy-four patients undergoing liver resection were randomized in a two-by-two factorial design to receive either postoperative magnesium hydroxide as a laxative, preoperative carbohydrate loading and postoperative ONS, their combination or a control group. Patients were managed within an ERAS programme of care. The primary outcome measure was time to first passage of stool. Secondary outcome measures were gastric emptying, postoperative oral calorie intake, time to functional recovery and length of hospital stay.**

**Results:** **Sixty-eight patients completed the trial. The laxative group had a significantly reduced time to passage of stool: median (interquartile range) 4 (3–5) *versus* 5 (4–6) days ($P = 0{\cdot}034$). The ONS group showed a trend towards a shorter time to passage of stool ($P = 0{\cdot}076$) but there was no evidence of interaction in patients randomized to the combination regimen. Median length of hospital stay was 6 (4–7) days. There were no differences in secondary outcomes between groups.**

**Conclusion:** **Within an ERAS protocol for patients undergoing liver resection, routine postoperative laxatives result in an earlier first passage of stool but the overall rate of recovery is unaltered. Registration number: NCT00538954 (http://www.clinicaltrials.gov).**

Paper accepted 9 March 2010

Published online 26 May 2010 in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.7120

## Introduction

If left unchecked, the metabolic response after abdominal surgery can result in prolonged recovery, increased morbidity and a longer hospital stay[1,2]. Enhanced recovery after surgery (ERAS) programmes combine interventions that target the elements that delay recovery: pain, gastrointestinal dysfunction and immobility[3]. Such protocols are safe, effective, accelerate recovery and reduce hospital stay following liver resection[4], aortic aneurysm repair[5], oesophagectomy[6] and colorectal resection[7–9].

Evidence for the efficacy of individual protocol elements within an ERAS programme is often extrapolated from traditional care[3]. Morbidity and hospital stay are relatively predictable after liver resection, which provides a suitable model for testing the individual elements within the ERAS protocol[10–12].

Reduced gastrointestinal function is a major factor that limits the success of enhanced recovery. Current protocols employ a multimodal package including continuous thoracic epidural anaesthesia, enforced mobilization, avoidance of excessive saline and early feeding which, in

traditional perioperative care, can reduce postoperative ileus[13–15] or promote earlier passage of stool[16]. Administration of magnesium hydroxide has been described in an unblinded, non-randomized study and employed in ERAS programmes[17]; however, despite widespread use of laxatives there is limited evidence to justify their routine postoperative use[7,17]. Preoperative carbohydrate loading may also promote earlier return of gastrointestinal function[18]. Within an ERAS protocol, carbohydrate loading and early oral nutritional supplements (ONS) may interact with laxatives to enhance gastrointestinal recovery further.

Early gastrointestinal recovery allows early oral intake, discontinuation of intravenous fluids and accelerated recovery. Early food intake may attenuate postoperative catabolism. Oral carbohydrate loading before surgery can also reduce this catabolic response and abate insulin resistance[19,20]. By improving the response to anabolic stimuli in the postoperative period, metabolic preconditioning may promote greater benefit from early nutritional intake. The perioperative administration of ONS has been shown to improve nutritional status and reduce minor complications within traditional perioperative care[21,22]. It is not known whether the provision of combined metabolic conditioning/early oral nutritional support along with early recovery of gastrointestinal function achieved with magnesium hydroxide can promote more rapid overall recovery within an ERAS protocol.

The aim of the Optimized Recovery with Accelerated Nutrition and Gastrointestinal Enhancement (ORANGE) study was to determine, within an ERAS protocol designed for hepatic resection, whether postoperative bowel stimulation with magnesium hydroxide and/or metabolic conditioning/ONS are effective in promoting early return of gastrointestinal function and overall postoperative recovery.

## Methods

This prospective randomized controlled trial with a two-by-two factorial design was conducted with the approval of Lothian Research Ethics Committee and the Ethics Committee of Maastricht University Medical Centre. Patients gave their written informed consent to participate. All were between the ages of 18 and 80 years, and scheduled to undergo hepatic resection for benign or malignant conditions at the Liver Unit, Royal Infirmary, Edinburgh, UK, or Maastricht University Medical Centre, The Netherlands, between July 2006 and June 2008. Patients with a body mass index of less than 18 or greater than 30 kg/m$^2$, pre-existing conditions limiting mobility, underlying cirrhotic liver disease, a history of liver resection, and those in whom bile duct excision and central or extended hepatectomy was planned before randomization, were excluded.

Recruitment took place during preoperative assessment at least 1 week before admission, allowing a period of reflection before obtaining consent. Patients received information packs and counselling related to the ERAS programme, highlighting early mobilization and early oral intake.

### Trial protocol

Patients were randomized to one of four groups (control, laxatives, ONS and laxatives + ONS). Randomization was performed using sealed opaque envelopes created in advance through block randomization with a random numbers table. Owing to the nature of the study interventions (nutritional supplements available in a variety of flavours to encourage compliance and magnesium hydroxide suspension produced by the hospital pharmacy), a suitable placebo was not feasible and so the type of treatment could not be masked. Patients randomized to laxatives received 1 g magnesium hydroxide orally twice daily from the day of surgery until discharge. Patients randomized to ONS received 800 ml oral carbohydrate loading drink (Nutricia Preop®; Nutricia Clinical Care, Trowbridge, UK.) at 22.00 hours the night before surgery and 400 ml at 06.00 hours on the morning of surgery. In addition, they received ONS (two cartons per day comprising 400 ml, 600 kcal, 24 g protein, Nutricia Fortisip®; Nutricia Clinical Care) from the day of surgery until day 30. Patients randomized to the laxatives + ONS group received the combined regimen.

A standardized perioperative and anaesthetic regimen, based on a previous ERAS protocol, was followed[3]. This multimodal, enhanced recovery programme was modified to cover all aspects of liver resection[4]. Notably, liver tissue sealant (TachoSil®; Nycomed, Zurich, Switzerland) was used to minimize bile leakage and haematoma formation, routine perihepatic drainage was avoided and paracetamol was used at the discretion of the surgeon in cases of extended resection. Patients were normally scheduled for surgery in the morning and were nursed in a high-dependency unit. Details of the ERAS liver protocol are shown in *Table 1*.

Seven surgeons performed all resections between the two centres. The extent of resection was classified according to the Brisbane 2000 Terminology[23]. Subcostal incisions were used and the transection plane determined by preoperative imaging and use of intraoperative ultrasonography. Resection was performed using a Cavitron Ultrasonic Surgical Aspirator (CUSA®; Valleylab, Boulder, Colorado, USA) and argon beam coagulation. The raw surface of the

**Table 1** Care plan for patients undergoing liver resection within an enhanced recovery after surgery protocol

| |
|---|
| Day before surgery |
| Normal feeding until midnight |
| No preanaesthetic medication |
| Day of surgery |
| Mid-thoracic epidural analgesia (local anaesthetic and low-dose opioid) |
| Short-acting anaesthetic agent |
| No nasogastric tube (removed immediately after surgery, if used) |
| Warm intravenous fluids and body warming device |
| Avoidance of excessive intravenous fluids |
| No routine drainage of peritoneal cavity |
| Free oral intake of water/nutrition started immediately |
| Patient out of bed for 2 h |
| Day 1 after surgery |
| Patient mobilized |
| Intravenous fluids discontinued |
| Patient to drink at least 1 litre of fluid |
| Normal diet |
| Continue mid-thoracic epidural analgesia |
| Paracetamol 1 g four times daily |
| Day 2 after surgery |
| Continue mid-thoracic epidural analgesia |
| Paracetamol 1 g four times daily |
| Normal diet |
| Patient mobilized |
| Day 3 after surgery |
| Stop epidural |
| Commence NSAIDs if appropriate |
| Remove urinary catheter |
| Encourage full oral intake and mobilization |
| Review discharge criteria |
| Day 4 after surgery |
| Encourage full oral intake and mobilization |
| Review discharge criteria |

NSAID, non-steroidal anti-inflammatory drug.

liver remnant was subjected to argon beam coagulation and sealed with TachoSil®. Abdominal drains were not placed routinely and the abdomen was closed with a standard running suture.

Study data were documented prospectively during the hospital stay and 30 days after surgery at an outpatient visit. Return of gastrointestinal function was determined by the first passage of stool after surgery. Patients were assessed for return of gastrointestinal function (passage of flatus/stool) on a daily basis. Secondary outcomes were: gastric emptying rate on day 3 after operation as determined by stable isotope breath test, postoperative oral nutritional intake on days 1–3 after surgery, functional recovery and length of stay.

## Stable isotope gastric emptying breath test

On the third day after surgery and following an overnight fast, some patients in one centre underwent assessment of gastric emptying rate by means of a non-invasive stable isotope breath test. This employed a 200-ml liquid test meal (Nutricia Fortisip®) containing a stable isotope tracer (75 mg sodium 1-[$^{13}$C]acetate)[24]. Breath samples were collected before and at predetermined intervals following consumption of the test meal. During the test period, activity was restricted to allow control and estimation of the rate of elimination of carbon dioxide[25]. The [$^{13}$C]carbon dioxide enrichment of breath samples ($^{13}$C : $^{12}$C ratio) was measured by automated continuous-flow isotope ratio mass spectrometry[26]. Raw data were subjected to curve fitting[27] to derive the half-time ($T_{1/2}$) of [$^{13}$C]carbon dioxide appearance in breath. The $T_{1/2}$ for gastric emptying was estimated using a 'self-correcting' model[28] that accounts for the delayed expiration of [$^{13}$C]carbon dioxide owing to pooling within the body's bicarbonate system.

## Oral nutritional intake

A senior dietician, in cooperation with the patient and ward nursing staff, recorded daily postoperative oral intake on a standard diet sheet. This was converted to energy intake (in kilocalories) and the recommended nutritional intake (RNI) was estimated using CompEat Pro® for Windows® (Nutrition Systems, Banbury, UK). The percentage RNI achieved on the first 3 days after surgery for each subject was used in comparisons between study groups.

## Functional recovery criteria

Functional recovery was defined as adequate pain control requiring only oral analgesia, adequate oral intake with no intravenous fluid requirement, independent mobility sufficient to perform activities of daily living, and blood results (liver function tests and inflammatory markers) returning towards normal ranges[4]. Criteria were assessed on a daily basis. An experienced clinician determined readiness for hospital discharge. Time to achieve functional recovery, initial length of stay (defined as number of nights in hospital after surgery, excluding readmissions) and all adverse events up to 30 days were recorded. Morbidity was documented prospectively according to criteria described previously[29,30]. Other data recorded for each patient included mortality, readmissions and use of preoperative chemotherapy.

## Statistical analysis

Retrospective data (P. O. Hendry and K. C. H. Fearon, unpublished results) indicated that the mean(s.d.) time to passage of stool was 5·3(1·3) days. This study was powered

($\alpha = 0{\cdot}05$, $\beta = 0{\cdot}80$) to detect a 20 per cent difference in time to passage of stool, the primary outcome. Based on this calculation, 14 patients were required in each of the four groups (56 patients overall). The secondary endpoints were of an exploratory nature. Continuous data were expressed as median (interquartile range). For comparison between study groups, data were analysed using Mann–Whitney *U* test, $\chi^2$ test or Fisher's exact test, as appropriate. $P < 0{\cdot}050$ was considered statistically significant. SPSS® version 17.0 for Mac® (SPSS, Chicago, Illinois, USA) was used for data analysis.

## Results

Between July 2006 and June 2008, 74 patients were recruited and randomized, 66 in Edinburgh and eight in Maastricht. Six patients did not undergo hepatic resection and were excluded. The remaining 68 patients were managed within the ORANGE protocol (*Fig. 1*).

Demographic data for the four groups are shown in *Table 2*. Overall the male to female ratio was 4:3 and median age was 62 (53–69) years. Sixty-two patients (91 per cent) were treated for malignant disease, and there were 53 major and 15 minor resections (*Table 3*). There were no significant differences across the study groups in sex, body mass index, American Society of Anesthesiologists grade, pathology, malignancy, use of neoadjuvant therapy or extent of liver resection.

Time to functional recovery and initial length of hospital stay were 4 (3–5) and 6 (4–7) days respectively, and were not significantly different between groups. The postoperative morbidity rate was 25 per cent overall, and did not differ significantly between the groups. Two patients required reoperation owing to postoperative haemorrhage. Five patients required readmission to hospital (intra-abdominal collection, 2; severe constipation, 1; bile leak, 1; pneumonia, 1). There were two deaths from myocardial infarction within 30 days of surgery (*Table 4*). Discharge from hospital was delayed in some patients for reasons outlined in *Table 5*.

Oral fluid intake was resumed on the day of surgery in 94 per cent of patients. Reintroduction of diet was achieved on day 1 in 37 per cent and by day 2 in

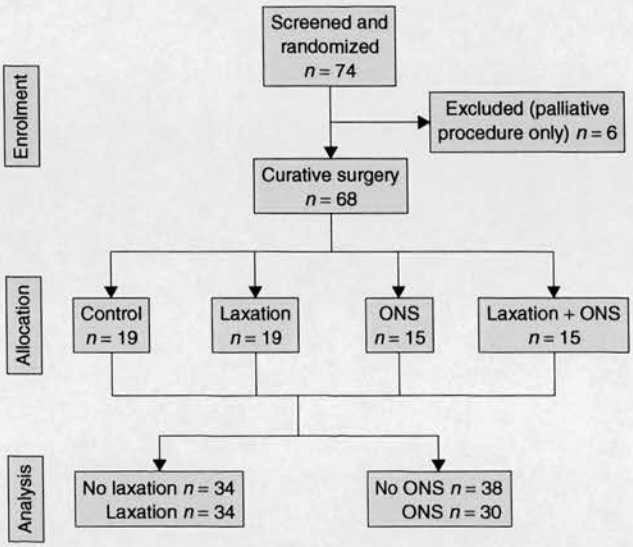



**Fig. 1** CONSORT diagram for the trial. ONS, oral nutritional supplements

**Table 2** Demographic and clinical data

| | | Laxatives | | | Oral nutritional supplements | | |
|---|---|---|---|---|---|---|---|
| | Overall ($n = 68$) | No ($n = 34$) | Yes ($n = 34$) | *P* | No ($n = 38$) | Yes ($n = 30$) | *P* |
| Age (years)* | 62 (53–69) | 62 (51–70) | 61·5 (55–69) | 0·722† | 65 (51–70) | 61 (52–63) | 0·243† |
| Sex ratio (M : F) | 38 : 30 | 21 : 13 | 17 : 17 | 0·464‡ | 20 : 18 | 18 : 12 | 0·626‡ |
| ASA grade | | | | | | | |
| I | 15 (22) | 7 (21) | 8 (24) | | 9 (24) | 6 (20) | |
| II | 43 (63) | 20 (59) | 23 (68) | | 23 (61) | 20 (67) | |
| III | 10 (15) | 7 (21) | 3 (9) | 0·391‡ | 6 (16) | 4 (13) | 0·973‡ |
| Body mass index (kg/m$^2$)* | 25 (23–28)¶ | 25 (23–31) | 25 (22–28) | 0·394† | 25 (22–28) | 25 (23–29) | 0·882† |
| Pathology | | | | | | | |
| Malignant disease | 62 (91) | 30 (88) | 32 (94) | 1·000‡ | 35 (92) | 27 (90) | 1·000‡ |
| Colorectal liver metastases | 56 (82) | 26 (76) | 30 (88) | | 31 (82) | 25 (83) | |
| Other metastatic disease | 6 (9) | 4 (12) | 2 (6) | | 4 (11) | 2 (7) | |
| Benign disease | 6 (9) | 4 (12) | 2 (6) | 0·445‡ | 3 (8) | 3 (10) | 0·829‡ |
| Neoadjuvant therapy | 22 (32) | 9 (26) | 13 (38) | 0·127‡ | 13 (34) | 9 (30) | 0·797‡ |

Values in parentheses are percentages unless indicated otherwise; *values are median (interquartile range). ASA, American Society of Anesthesiologists. †Mann–Whitney *U* test; ‡$\chi^2$ test. ¶Correction added after online publication 26 May 2010: Body mass index 22 (23–28) was corrected to 25 (23–28).

**Table 3** Extent of liver resection

| | | Laxatives | | | Oral nutritional supplements | | |
|---|---|---|---|---|---|---|---|
| | Overall ($n = 68$) | No ($n = 34$) | Yes ($n = 34$) | $P$* | No ($n = 38$) | Yes ($n = 30$) | $P$* |
| Major (trisectionectomy, central hepatectomy, hemihepatectomy) | 53 | 25 | 28 | | 31 | 22 | |
| Minor (sectionectomy, segmentectomy, metastasectomy) | 15 | 9 | 6 | 0·560 | 7 | 8 | 0·557 |

Values in parentheses are percentages. *Fisher's exact test.

**Table 4** Outcome data

| | | Laxatives | | | Oral nutritional supplements | | |
|---|---|---|---|---|---|---|---|
| | Overall ($n = 68$) | No ($n = 34$) | Yes ($n = 34$) | $P$ | No ($n = 38$) | Yes ($n = 30$) | $P$ |
| Time to first drink* | 0 (0–0) | 0 (0–0) | 0 (0–0) | 1·000† | 0 (0–0) | 0 (0–0) | 0·808† |
| Time to first food* | 1 (1–1) | 1 (0–1) | 1 (0–1) | 0·218† | 1 (0–1) | 1 (0–1) | 0·499† |
| Time to first flatus* | 3 (2–4) | 3 (2–4) | 2·5 (2–3·5) | 0·108† | 3 (2–5) | 3 (2–4) | 0·262† |
| Time to first stool* | 5 (4–6) | 5 (4–6) | 4 (3–5) | 0·034† | 5 (4–7) | 4 (3–5) | 0·076† |
| Time to functional recovery* | 4 (3–5) | 4 (3–4·5) | 4 (3–5) | 0·242† | 4 (3–5) | 4 (3–4) | 0·110† |
| Initial hospital stay* | 6 (4–7) | 5 (4–6) | 6 (5–8) | 0·081† | 6 (5–7) | 5 (4–7) | 0·367† |
| Readmission | 5 (7) | 3 (9) | 2 (6) | 1·000§ | 3 (8) | 2 (7) | 1·000§ |
| Reoperation | 2 (3) | 1 (3) | 1 (3) | 1·000§ | 2 (5) | 0 (0) | 0·504§ |
| 30-day morbidity | 17 (25) | 8 (24) | 9 (26) | 1·000§ | 11 (29) | 6 (20) | 0·574§ |
| 30-day mortality | 2 (3) | 2 (6) | 0 (0) | 0·494§ | 2 (5) | 0 (0) | 0·500§ |

Values in parentheses are percentages unless indicated otherwise; *values are median (interquartile range). †Mann–Whitney $U$ test; §Fisher's exact test.

**Table 5** Reasons for delayed discharge

| | No. of patients |
|---|---|
| Caution owing to earlier complication or extensive surgery | 5 |
| Patient not confident to be discharged | 4 |
| Transport or social problems | 2 |
| Patient boarded to another ward before discharge | 1 |
| Patient drowsy owing to analgesia | 1 |

91 per cent. Intravenous fluids were discontinued on day 1 in 51 per cent of patients and by day 2 in 78 per cent. Mid-thoracic epidural anaesthesia was commenced before surgery in 99 per cent of patients and continued for at least 48 h after operation in 93 per cent; four epidurals failed on day 1. Drains were used in nine patients (13 per cent). Nineteen patients (28 per cent) achieved mobilization on the day of surgery. Sixteen patients (24 per cent) had a urinary catheter in place beyond discontinuation of epidural analgesia and 32 (47 per cent) received non-protocol intravenous fluids in the perioperative period.

Overall, the median time to passage of stool was 5 (4–6) days. Patients randomized to ONS showed a trend towards a shorter time to passage of stool: 4 (3–5) *versus* 5 (4–7) days ($P = 0·076$). Those randomized to laxatives had a significantly reduced time to passage of stool: 4 (3–5) *versus* 5 (4–6) days ($P = 0·034$). Patients randomized to the combination regimen also had a significantly reduced time to passage of stool: 3 (3–4) *versus* 6 (4–7) days ($P = 0·013$). There was no evidence of interaction between laxatives and ONS (*Fig. 2*).

Thirty-two of 56 patients asked to participate in the gastric emptying protocol completed it (7 control, 10 laxative, 8 ONS, 7 laxative + ONS). Median postoperative gastric emptying ($T_{1/2}$) was 0·74 (0·46–1·41) h, with no significant difference between study groups. Five patients had significantly delayed gastric emptying ($T_{1/2}$ more than the 90th percentile of 1·69 h). In comparison with the remaining 27 patients who underwent measurement of gastric emptying rate, this group had a significantly prolonged hospital stay: 10 (7–11) *versus* 6 (5–7) days ($P = 0·019$).

Oral intake of at least 50 per cent of recommended nutritional requirement was achieved at a median of 1 (1–2) days after surgery for the whole group. This was not significantly different between groups. Total calorie intake (including ONS) on days 1–3 after surgery for those randomized to ONS was not significantly different from that in patients who did not receive ONS (*Fig. 3*). The median percentage change in bodyweight from preoperative level for all subjects was +1·82 (−1·41 to 5·82) and −2·01 (−4·65 to −0·34) per cent on days 5 and 30 respectively

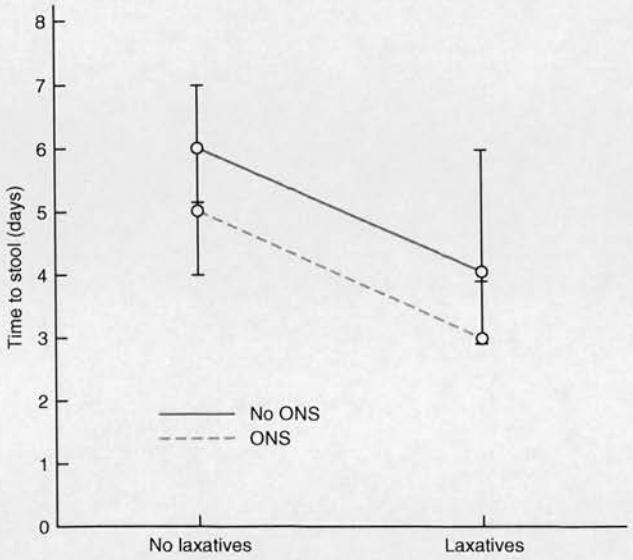



**Fig. 2** Interaction between laxatives and oral nutritional supplements (ONS). Values are median with interquartile range

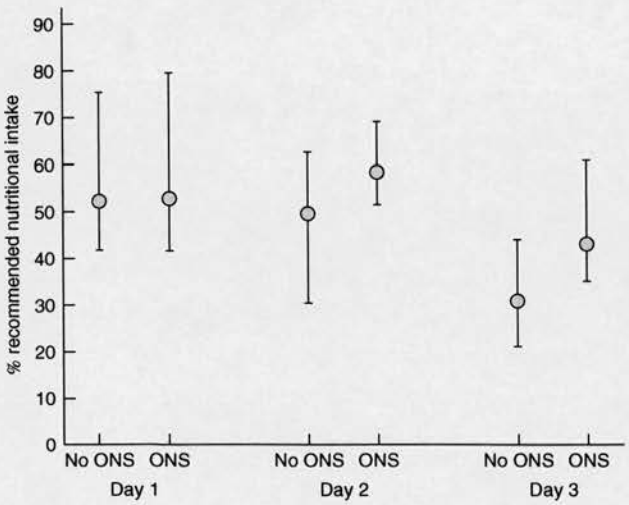



**Fig. 3** Total calorie intake during the first 3 days after surgery. Values are median with interquartile range. ONS, oral nutritional supplements

after surgery; there were no significant differences between groups ($P = 0{\cdot}166$ and $P = 0{\cdot}200$ respectively).

## Discussion

In this study, laxatives significantly decreased the time to passage of stool after liver surgery. Those randomized to the combination regimen also had a significantly reduced time to passage of stool, but with no evidence of interaction between laxatives and ONS. There were no differences in secondary outcomes between groups. These results are in keeping with previous findings[31,32].

Previous studies suggested that early restoration of food intake results in a more rapid return of gut function in the postoperative period[16]. In the present study, calorie intake (food plus ONS) of the group randomized to ONS was no different from that of patients who did not receive ONS, suggesting that ONS in the early postoperative phase suppressed normal food intake to the point at which there was no net benefit. The lack of interaction between laxatives and ONS could therefore be explained on the basis that ONS did not alter overall calorie intake. This would also explain the lack of effect of ONS on the secondary outcomes.

Patients following the ERAS protocol recommenced oral fluid on the day of surgery, started eating the following day, were mobile by the third day and achieved discharge criteria on the fourth day. Median hospital stay was 6 days, which is significantly shorter than the 8–14 days reported in other centres following traditional perioperative care[11,12,33,34]. This study provides further evidence to support the use of an ERAS pathway following liver resection to accelerate postoperative recovery and shorten length of stay. It remains unclear which components of reduced stay result from the introduction of a formal care pathway rather than the enhanced recovery elements of that pathway. In the present study, functional recovery was achieved a median of 4 days after surgery, a median of 2 days before discharge from hospital. It may be possible to achieve a shorter overall hospital stay by further tightening the care pathway elements of the protocol[35].

In this study, the overall morbidity rate was 25 per cent, with a readmission rate of 7 per cent and mortality rate of 3 per cent. Morbidity rates were lower and mortality rates in keeping with those published from other countries following traditional care (38–45 and 2·7–3·1 per cent respectively)[11,33,36].

All patients received preoperative counselling and there was a high level of compliance with most elements of the protocol. Ninety-nine per cent of patients received preoperative epidural anaesthesia. Intraoperative drainage was used only in patients considered to have a higher risk of bile leakage (13 per cent), in keeping with current evidence[37,38].

In the early postoperative period, adherence to the protocol was lower than in the preoperative and intraoperative phases, as in previous studies[35,39]. Intravenous fluids were discontinued on the day after surgery in only half of the patients. Saline (0·9 per cent) was often prescribed by out-of-hours medical staff, less familiar

with the study protocol. Only 28 per cent of patients were mobilized on the day of surgery; usual reasons for failure to achieve this were epidural-related hypotension or late return to the high-dependency unit. Future ERAS protocols may overcome the issue of late return to the ward by initiating mobilization in the recovery room. Postoperative variables are markers of both protocol compliance and recovery; patients achieving these protocol goals are those likely to achieve a faster recovery.

There were no significant differences between study groups in the rate of gastric emptying. The gastric emptying protocol was available for 56 patients in the study, but it was impractical for 15 and refused by nine patients. The absence of significant differences between the groups should be interpreted with caution. The use of a stable isotope gastric emptying breath test as a postoperative recovery marker is novel. Stable isotope gastric emptying breath testing[40,41] requires no specialist technical skills and is well tolerated. This is an inexpensive method for determining the gastric emptying rate and may be an objective marker of recovery in the early postoperative period. The limitations of the test may preclude it from being suitable for comparing subjects with rapid gastric emptying. It may be better suited to highlighting patients who have delayed gastric emptying and are likely to have a slower return to full diet, longer hospital stay and slower postoperative recovery. In the present protocol, day 3 after surgery was chosen for this test because the patients had returned to the ward. It would be of interest to study this variable at other time points.

Within the context of multimodal therapy it is difficult to separate the effect of one protocol component from another. A two-by-two factorial design is an efficient way of assessing two different factors and evaluating their potential interaction. The statistical design of the present study meant that there was a potential confounder in 50 per cent of each group under description; this reflects the exploratory nature of the evaluation of potential interactions.

The present study has shown that laxatives can hasten return of colonic function in patients undergoing hepatic resection. However, there was no evident interaction with ONS. More importantly, there seemed to be no benefit in terms of enhanced oral intake or overall recovery. Thus the benefit of routine laxatives or ONS is difficult to gauge. Clearly the present findings cannot be extrapolated directly to patients with an intestinal anastomosis. Future studies might also evaluate the interaction between the present variables and other measures designed to improve upper gastrointestinal function and oral intake.

## Collaborators

Members of ERAS Study Group were: S. F. F. W. Bukkems, C. H. C. Dejong and R. M. van Dam (Maastricht University Medical Centre and NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University, Maastricht, The Netherlands); K. C. H. Fearon, O. J. Garden, P. O. Hendry, D. W. McKeown and R. W. Parks (Royal Infirmary, Edinburgh, UK); J. Hausel and J. Nygren (Ersta Hospital, Stockholm, Sweden); R. Kennedy (Department of Surgery, Yeovil District Hospital, Yeovil, UK); K. Lassen (University Hospital Northern Norway and University of Tromsø, Tromsø, Norway); O. Ljungqvist (Karolinska Institute, Stockholm, Sweden); D. N. Lobo (Queen's Medical Centre, Nottingham, UK); J. Maessen and M. F. von Meyenfeldt (University Hospital Maastricht, Maastricht, The Netherlands); T. Preston (Scottish Universities Environmental Research Centre, East Kilbride, UK); A. Revhaug (University Hospital Northern Norway, Tromsø, Norway); C. Spies (University Medicine Berlin, Berlin, Germany).

## Acknowledgements

The authors thank C. Graham and G. Murray for statistical advice in the preparation of this manuscript, the patients who agreed to participate in the study, and the surgeons, anaesthetists and nursing colleagues who helped implement the protocol: E. Hidalgo, K. K. Madhavan, J. Powell, R. Ravindran, S. Wigmore, B. Cook, D. Cameron and A. Lee in the UK; M. H. A. Bemelmans, P. B. W. Cox and G. J. P. Breukelen in the Netherlands. They also thank K. Yuill, A. C. Small, L. Kirkpatrick, A. Balfour and D. Francart who played a key role in implementation of the protocol and collection of the primary prospective data. Nutricia Preop® (Nutricia Nutridrink® in The Netherlands) and Nutricia Fortisip® drinks were supplied by Nutricia Clinical Care (Trowbridge, UK) and Nutricia Nederland (Advanced Medical Nutrition, Zoetermeer, The Netherlands). The authors declare no other conflict of interest.

## References

1 Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000; **85**: 109–117.
2 Nygren J, Hausel J, Kehlet H, Revhaug A, Lassen K, Dejong C *et al.* A comparison in five European Centres of case mix, clinical management and outcomes following either conventional or fast-track perioperative care in colorectal surgery. *Clin Nutr* 2005; **24**: 455–461.
3 Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K *et al.* Enhanced recovery after surgery:

a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr* 2005; **24**: 466–477.
4 van Dam RM, Hendry PO, Coolsen MM, Bemelmans MH, Lassen K, Revhaug A *et al.* Initial experience with a multimodal enhanced recovery programme in patients undergoing liver resection. *Br J Surg* 2008; **95**: 969–975.
5 Podore PC, Throop EB. Infrarenal aortic surgery with a 3-day hospital stay: a report on success with a clinical pathway. *J Vasc Surg* 1999; **29**: 787–792.
6 Cerfolio RJ, Bryant AS, Bass CS, Alexander JR, Bartolucci AA. Fast tracking after Ivor Lewis esophagogastrectomy. *Chest* 2004; **126**: 1187–1194.
7 Basse L, Hjort Jakobsen D, Billesbølle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg* 2000; **232**: 51–57.
8 Wind J, Polle SW, Fung Kon Jin PH, Dejong CH, von Meyenfeldt MF, Ubbink DT *et al.* Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg* 2006; **93**: 800–809.
9 Walter CJ, Collin J, Dumville JC, Drew PJ, Monson JR. Enhanced recovery in colorectal resections: a systematic review and meta-analysis. *Colorectal Dis* 2009; **11**: 344–353.
10 Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg* 2000; **191**: 38–46.
11 Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S *et al.* Improvement in perioperative outcome after hepatic resection: analysis of 1803 consecutive cases over the past decade. *Ann Surg* 2002; **236**: 397–406.
12 Dimick JB, Wainess RM, Cowan JA, Upchurch GR Jr, Knol JA, Colletti LM. National trends in the use and outcomes of hepatic resection. *J Am Coll Surg* 2004; **199**: 31–38.
13 Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; **359**: 1812–1818.
14 Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 2005; **103**: 25–32.
15 Fotiadis RJ, Badvie S, Weston MD, Allen-Mersh TG. Epidural analgesia in gastrointestinal surgery. *Br J Surg* 2004; **91**: 828–841.
16 Stewart BT, Woods RJ, Collopy BT, Fink RJ, Mackay JR, Keck JO. Early feeding after elective open colorectal resections: a prospective randomized trial. *Aust N Z J Surg* 1998; **68**: 125–128.
17 Fanning J, Yu-Brekke S. Prospective trial of aggressive postoperative bowel stimulation following radical hysterectomy. *Gynecol Oncol* 1999; **73**: 412–414.
18 Noblett SE, Watson DS, Huong H, Davison B, Hainsworth PJ, Horgan AF. Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. *Colorectal Dis* 2006; **8**: 563–569.
19 Soop M, Nygren J, Myrenfors P, Thorell A, Ljungqvist O. Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. *Am J Physiol Endocrinol Metab* 2001; **280**: E576–E583.
20 Nygren J, Soop M, Thorell A, Efendic S, Nair KS, Ljungqvist O. Preoperative oral carbohydrate administration reduces postoperative insulin resistance. *Clin Nutr* 1998; **17**: 65–71.
21 Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. *Gut* 2000; **46**: 813–818.
22 Smedley F, Bowling T, James M, Stokes E, Goodger C, O'Connor O *et al.* Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *Br J Surg* 2004; **91**: 983–990.
23 Terminology Committee of the International Hepato-Pancreato-Biliary Association. IHPBA Brisbane 2000 terminology of liver anatomy and resections. *HPB Surg* 2000; **2**: 333–339.
24 Braden B, Adams S, Duan LP, Orth KH, Maul FD, Lembcke B *et al.* The [$^{13}$C]acetate breath test accurately reflects gastric emptying of liquids in both liquid and semisolid test meals. *Gastroenterology* 1995; **108**: 1048–1055.
25 Slater C, Preston T, Weaver LT. Comparison of accuracy and precision of heart rate calibration methods to estimate total carbon dioxide production during $^{13}$C-breath tests. *Eur J Clin Nutr* 2006; **60**: 69–76.
26 Preston T, McMillan DC. Rapid sample throughput for biomedical stable isotope tracer studies. *Biomed Environ Mass Spectrom* 1988; **16**: 229–235.
27 Siegel JA, Urbain JL, Adler LP, Charkes ND, Maurer AH, Krevsky B *et al.* Biphasic nature of gastric emptying. *Gut* 1988; **29**: 85–89.
28 Bluck LJ, Coward WA. Measurement of gastric emptying by the $^{13}$C-octanoate breath test – rationalization with scintigraphy. *Physiol Meas* 2006; **27**: 279–289.
29 Lång M, Niskanen M, Miettinen P, Alhava E, Takala J. Outcome and resource utilization in gastroenterological surgery. *Br J Surg* 2001; **88**: 1006–1014.
30 Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg* 1991; **78**: 355–360.
31 Zingg U, Miskovic D, Pasternak I, Meyer P, Hamel CT, Metzger U. Effect of bisacodyl on postoperative bowel motility in elective colorectal surgery: a prospective, randomized trial. *Int J Colorectal Dis* 2008; **23**: 1175–1183.
32 Hansen CT, Sørensen M, Møller C, Ottesen B, Kehlet H. Effect of laxatives on gastrointestinal functional recovery in fast-track hysterectomy: a double-blind, placebo-controlled randomized study. *Am J Obstet Gynecol* 2007; **196**: 311.e1–7.
33 Petrowsky H, McCormack L, Trujillo M, Selzner M, Jochum W, Clavien PA. A prospective, randomized, controlled trial comparing intermittent portal triad clamping *versus* ischemic preconditioning with continuous clamping for major liver resection. *Ann Surg* 2006; **244**: 921–928.

34 Capussotti L, Muratore A, Ferrero A, Massucco P, Ribero D, Polastri R. Randomized clinical trial of liver resection with and without hepatic pedicle clamping. *Br J Surg* 2006; **93**: 685–689.

35 Maessen J, Dejong CH, Hausel J, Nygren J, Lassen K, Andersen J *et al.* A protocol is not enough to implement an enhanced recovery programme for colorectal resection. *Br J Surg* 2007; **94**: 224–231.

36 Nikfarjam M, Shereef S, Kimchi ET, Gusani NJ, Jiang Y, Avella DM *et al.* Survival outcomes of patients with colorectal liver metastases following hepatic resection or ablation in the era of effective chemotherapy. *Ann Surg Oncol* 2009; **16**: 1860–1867.

37 Fong Y, Brennan MF, Brown K, Heffernan N, Blumgart LH. Drainage is unnecessary after elective liver resection. *Am J Surg* 1996; **171**: 158–162.

38 Burt BM, Brown K, Jarnagin W, DeMatteo R, Blumgart LH, Fong Y. An audit of results of a no-drainage practice policy after hepatectomy. *Am J Surg* 2002; **184**: 441–445.

39 Hendry P, Hausel J, Nygren J, Lassen K, Dejong CH, Ljungqvist O *et al.* Determinants of outcome after colorectal resection within an enhanced recovery programme. *Br J Surg* 2009; **96**: 197–205.

40 Ghoos YF, Maes BD, Geypens BJ, Mys G, Hiele MI, Rutgeerts PJ *et al.* Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. *Gastroenterology* 1993; **104**: 1640–1647.

41 Perri F, Clemente R, Festa V, Quitadamo M, Niro G, Andriulli A. $^{13}$C-octanoic acid breath test: a reliable tool for measuring gastric emptying. *Ital J Gastroenterol Hepatol* 1998; **30**: 211–217.